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THE BEHAVIOR OF THE TESTIS IN TRANSPLANTATION, EXPERIMENTAL CRYPTORCHIDISM, VASECTOMY, SCROTAL INSULATION, AND HEAT APPLICATION.*

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A realization of the remarkable influences of sex hormones on the differentiation of the genital complex in cattle discovered by Professor F. R. Lillie (1) led him to initiate a concerted program of sex research in the laboratories of Zoology at the University of Chicago looking to the development of our knowledge of the fundamental problems in the biology of sex. The work has been in progress now for some seven years and at the present time is being actively carried forward along many divergent lines.

It was at Professor Lillie's suggestion that I took up the study of some phases of the sex biology of mammals and it is a pleasure to be able at this time to present some of the results obtained from work on the mammalian testis.† While not em-

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phasizing directly the aspects of its internal secretions the work deals with many basic problems from which have been built up much of our present-day conceptions of the internal secretions of the testes. I hope the knowledge gained, and the problems discussed, may be of such a nature that a consideration from the viewpoint of this presentation may not appear entirely out of place in a meeting of this society.

Considering first testis grafting, or transplantation, I have only to mention the work of Steinach, Sand, and others whom I will not now name, to recall its importance particularly as it relates to present conceptions of the elements so far believed to be the source of testis hormones. The classical picture of a mammalian testis graft recovered some time after transplantation is given to us as follows: The seminiferous tubules are well outlined by the connective tissue basement membrane, but are usually smaller in caliber than those of normal testes. The content of these tubules consists usually of a single layer of cells located next the basement membrane, the Sertoli cells, often the sole remains of the former germinal epithelium. The tubules, again unlike those of normal testes, are widely separated and the interstices packed with interstitial cells or cells of Leydig and some connective tissue; such a condition of the interstitial tissue has usually been interpreted as an hypertrophy of the cells of Leydig. Since the interstitial tissue is present in an apparent overabundance, the germinal epithelium almost entirely absent, and the Sertoli cells being usually denied a secretory function, many have been led to conclude that the source of the internal secretion of the testis must reside in the interstitial tissue.

I have obtained many testis grafts from rat and guinea pig transplantations that were similar to the above type of graft, but also many that were radically unlike it, and it is to these latter that I would direct your attention for a brief moment. Rat testis grafts have been recovered after transplantation into normal males, castrated males, normal virgin females, castrated females, and females that had delivered normal litters of young, having carried the transplanted testis some months before and during the pregnancy. The idea of the "Antagonism of Sex Hormones" postulated by Steinach to account for his failure

to obtain growth of transplanted testes in females possessing their normal ovaries, and forming the basis of much of his work of the past ten years, as well as the "Atreptical Immunity" hypothesis of the Danish investigator, Knud Sand, formulated to account for the same lack of persistence of testes transplanted subcutaneously into females with ovaries, must, I feel, be discarded. But it is the character of the testis grafts, recovered from subcutaneous, intramuscular, and intraperitoneal positions, I wish most to emphasize.

Many of the grafts, instead of containing seminiferous tubules devoid of germinal cells, have contained tubules with a fairly complete germinal epithelium, many cells of which are in stages of mitosis; two or even three rows of cells may be adhering together sufficiently to build up an epithelium. The curious fact remains, however, that differentiated spermatozoa have never been found in grafts residing in these localities in the animal body. The germinal cells actively divide and produce new cells, but those cells nearest the lumen of the tubule become loosened from the epithelium, escape into the lumen and undergo degeneration. The question is pertinent, Why is not complete germ cell differentiation realized? It has been a problem since first mammalian testes were transplanted to account for the lack of spermatozoa in the testis grafts. Different again from the usual picture of a testis graft the interstitial tissue is not overdeveloped and in fact is not different from that of the normal testis.

A great deal of light has been cast upon the behavior of a graft by a relatively detailed study of experimental cryptorchidism. It has been known for longer than a century that man and other mammals occasionally experience a retention of one or both testes in the peritoneal cavity, one in five hundred military recruits, according to Bevan (2). The structure of such undescended or cryptorchid testes has been described for man, pig, sheep, horse, and other mammals and it is known that not only is bilateral cryptorchidie, or double peritoneal retention of the testes, followed by sterility, but also that such testes are devoid of germinal cells excepting possibly a few spermatogonia; the seminiferous tubule intervals are usually packed with an

apparent over-abundance of interstitial cells. In short, such a testis is quite similar to the usually described testis graft.

The guinea pig, rat, rabbit, and some other mammals retain throughout life a wide open connection between the scrotum and the peritoneal cavity, and by contraction of muscles in connection with the scrotal sac the testes may be elevated through the open inguinal canals into the abdominal cavity, to redescend into the scrotum on relaxation of the latter structure. Under these conditions the testes are normal. If, however, the testes are pushed through the open inguinal canals into the peritoneal cavity and are prevented from returning to the scrotum a very rapid and striking, progressive, degeneration of the generative portion follows. Forcible retention may be accomplished by several slightly different means, i. e., by severing the mesenterial gubernacular connection between the epididymis and the bottom of the scrotum and turning the testis back into the peritoneal cavity; by pushing the testis through the canals and tying the scrotum, or sewing shut the inguinal canals, etc. Under such conditions the blood supply, nerve connections and vas deferens are normal. More certainly will the testis be retained in the abdomen if the inguinal canals are closed with a purse string structure, but in approximately 50 per cent of the cases in the guinea pig the testes do not redescend into the scrotum when the canals remain open, even though the testes are not fastened by sutures.

It makes little difference what means are taken to insure abdominal retention of the elevated testis, the results are the same if the organ does not sag into the inguinal canal. The germinal epithelium of a normal active testis retained for the short period of seven days in the abdomen will be found to be totally disorganized. The usually well defined tubular lumen will be practically filled with a mass of free cells thrown out from the epithelium; many cells may appear approximately normal, but the majority are in a stage of degeneration. Some of the cells can be defined in outline only, others show fragmentation of the nucleus, and chromatin materials scattered throughout the cell or protoplasmic masses may be located in a granular debris, the result of more extensive degeneration. The former compact epithelium is little in evidence, its place

having been taken by a fibrillar reticulum filled with vacuoles or spaces from which the cells have escaped or in which they have undergone fragmentation and dissolution, with or without the complete removal of the fragmented remains. Very often large multinuclear protoplasmic masses—typical "giant cell" like masses—are to be found either in the epithelial position or loose in the lumen. All stages in the formation of these multinucleate masses can be followed and they are seen to owe their origin to the coalescence of contiguous germinal cells; the cell walls disappear and the epithelium reminds one of the proverbial melting pot in which discrete cells are merged into a common protoplasmic mass.

After fourteen days' peritoneal retention the majority of the degenerating debris has been removed from the tubules through liquefaction and transportation and but few cells can be seen; these are almost without exception in a degenerate condition. By twenty days little remains in the tubules, aside from the reticulum, than the Sertoli cells situated against the inner border of the basement membrane, and a few spermatogonia. We have, therefore, produced experimentally within twenty days, a typical cryptorchid testis such as occurs in nature.

So long as the testis remains in the peritoneal cavity it is degenerate. Followed at brief intervals from seven days to more than a year after operation, the testes are found to decrease progressively in size; tubules shrink to one-third their original diameter and interstitial cells become more prominent and are collected in masses between the now more widely separated tubules. If by chance the testis returns to the scrotum after being elevated into the peritoneal cavity it may be found a few months later in a normal condition. If descent has been only partial, and the testis is held by adhesions from taking its normal scrotal position, then the testis may be in part normal, part degenerate. In general it may be stated that the more nearly a testis returns to its normal scrotal position the more nearly normal will be the seminiferous tubule epithelium.

To test the powers of recuperation of a testis after degeneration, both testes of an animal were elevated to the peritoneal cavity and so retained for twenty-four days. By a second operation one testis was replaced in the scrotum, the opposite one

removed and studied histologically to ascertain the stage of degeneration of the one in the scrotum. The seminiferous tubules, at the end of twenty-four days are empty of all degenerating remains, and Sertoli cells with a small number of spermatogonia form a single layer of cells against the walls of the basement membrane.

It can be realized, therefore, that the testis replaced in the scrotum, after its twenty-four days' retention in the abdomen, was in a highly degenerate condition. It was allowed to remain in the scrotum for 2½ months, when the animal was killed and the testis prepared for histological study. The replaced testis had almost completely recovered from its degenerated condition. The majority of the tubules contained a well established epithelium and in many of them spermatozoa had again appeared, and these tubules were normal. A few tubules were in stages of partial recovery, but some were entirely devoid of epithelium. In the latter case it is questionable if recovery would have ever taken place and there is little doubt that all cells capable of further division were destroyed during the peritoneal confinement. The few totally degenerated tubules were located indiscriminately among normal tubules and not segregated off into any particular locality, thus showing that recovery had no definite relation to particular local conditions within the gonad, but depended upon the presence of cells capable of further division at the time of scrotal replacement.

It follows, therefore, that the scrotum exerts a peculiarly striking influence upon the testis and an influence that is necessary not only for the complete differentiation of germ cells but even for the retention of cells previously differentiated. Removed from the scrotum, or from conditions stimulating those of the scrotum, a testis is rapidly deprived of its germinal epithelium.

Is this not a partial solution for the absence of differentiated germ cells in testis grafts? With a realization that the testis-scrotal relationship is necessary for the production of spermatozoa I transplanted testes into the scrotum by sewing them to the walls of the tunica vaginalis. The idea proved correct for I have recovered testis grafts, from transplantation onto the scrotal walls six months previous, that contained normal semi-

niferous tubules with differentiated spermatozoa. Thus for the first time have testis grafts of mammals been obtained that contained normal seminiferous tubules. We have additional evidence in this result that the scrotum is necessary for germ cell differentiation in those mammals that normally possess a scrotum.

Approaching the general problem of testis reactions, this time following the effects of occluding the outlet duct or vas deferens by ligation, sometimes combined with resection of the duct, we discuss a problem that has been a point of controversy for more than fifty years, a controversy dealing not with a general interpretation of a series of phenomena but merely with the question whether testicular degeneration follows ligation of the vas deferens. Opinions in number are about equally divided between degeneration and lack of it, but due to the great influence of Bouin and Ancel (3), really the founders of the conception that the testicular hormones are derived from the interstitial cells, it has in late years been assumed that the problem was settled and that vas deferens ligation caused the testes to degenerate. The contrary contentions of earlier workers were dismissed by these two investigators, on the basis of observations made before a sufficient length of time had elapsed after vas deferens ligation. Following Steinach, the testes undergo degeneration, perhaps regenerate in many cases, but interstitial cell hypertrophy follows and we are asked to believe that rejuvenation and restoration of youthful qualities is accomplished by the operation; supermales are considered possible merely upon the basis of a great interstitial cell hypertrophy. Bouin and Ancel state that if one waits sufficiently long degeneration invariably follows vas deferens ligation. It should be noted, however, that in the absence of a definition of a *sufficient length of time* the statement cannot be disproved; degeneration undoubtedly follows in old age, and it is generally accepted that the sexual life of a rat and guinea pig is to be counted in a small number of years. With the above assertions Bouin and Ancel reproduce a drawing of a guinea pig testis 78 days after vas deferens ligation that was totally degenerate as concerns the germinal epithelium. Seventy-eight days should, therefore, be a sufficiently long time to wait for degeneration. In our lab-

oratory Dr. Oslund found that vas deferens ligation of ten months' duration in the rat and guinea pig was followed by perfectly normal testes (4). Some degenerate testes did occur in Oslund's material, but by no means sufficiently related in time intervals after operation to be due to the influence of the blocking of the vas deferens. Knowing the rapidity of degeneration with inguinal or peritoneal retention of the testes, he was able to correlate all cases of degeneration with an abnormal scrotal relationship of the testis, where the position of the latter was definitely noted at the time of its removal. An appreciation of the delicate relationship established with, and dependent upon, the scrotum leads to the belief that the instances of degeneration of other workers are due to testicular retention by adhesions in the inguinal canals or peritoneal cavity, or by some influence that removes the testis from its normal relationship with the scrotum.

I believe that if one appreciates the fact that a given number of animals having the vas deferens completely blocked for a period of, for example, four months, possess normal testes, but operations on the same type of animal in the hands of other workers result in degenerate testes in one-half the given time, we must conclude that degeneration is actually due not to the operation itself but to subsequent influences due in reality to other factors.

With the assistance of Mr. W. J. Quick I have recently studied the effects of vas deferens occlusion in the rabbit, an animal often employed for a study of this problem (5). We have studied the testis histologically from thirteen days after complete occlusion of the vas deferens (a time according to Steinach where degeneration takes place followed by regeneration) to longer than six months after the operation. During this period of time the seminiferous tubules are perfectly normal, the germ cells are in active mitosis and quantities of spermatozoa are present. Vas deferens occlusion does not cause the testes to degenerate in the rabbit within six months after the operation. Can we offer an attempt at a logical explanation of degeneration obtained in other laboratories? Oslund's work would appear to do so. It thus appears that displacement of the testis in reference to the scrotum, a situation not fully appreciated hereto-

fore, may account for a number of such cases. To compare with a testis having the vas deferens occluded, we have purposely allowed the opposite testis of an animal to exist with an abnormal scrotal relationship but with the vas deferens normal, i. e., not occluded. The former testis at the end of thirteen days is perfectly normal, whereas, the one with normal vas deferens but with abnormal scrotal relationships presents a testis lacking from one-half to three-forths of the germinal epithelium, lost through degeneration but with many of the remaining cells in a stage of mitosis. Is not such a testis, thirteen days after operation, in a condition that would easily fit the contentions of Steinach (6) or Tiedje (7) of a degeneration followed by regeneration? Surely the testis is highly degenerate, and just as certainly are mitotic figures abundant and the condition could easily be construed as regeneration changes. But here the vas deferens had not been occluded and we know that the influences were due to displacement from the normal scrotal environment. Adhesions following operation will bring about just such a result; they have sometimes been formed after our operations and have been mentioned by Sand.

But what of vas deferens occlusion of longer duration? In the twenty rabbit testes of our materials enlargements at the cut end of the vas deferens (spermatocysts), described by Oslund, Tiedje, and Sand and considered by some as a deterrent of testis degenerations, have never occurred. At three and one-half months after vasectomy and later, our materials have presented a pronounced and striking enlargement of the epididymis, the result of hypertrophy of this structure and due undoubtedly to the stimulus of the presence of testicular products brought to it from the continuously active seminiferous tubules. The epididymis at six months after vas occlusion has been noted to be twice or even three times its normal size. It is so large that one may detect immediately, on a superficial glance at the scrotum of a living rabbit, which one of the two testes has had the duct blocked; the contour of the epididymis impresses itself upon that of the scrotum due to its great distension.

Since a large part of the epididymis is located at the bottom of the scrotum, underneath the testis proper, and since the scrotum itself does not enlarge correspondingly, the effect is to dis-

place the testis upward into the open inguinal canal or even into the peritoneal cavity. The testis once having been forced through the canal into the abdomen is returned to the scrotum less easily than the normal testis with a smaller sized epididymis. One of our cases was found partially confined to the peritoneal cavity and here the testis was degenerate. Obviously it would be a misrepresentation to attribute this degeneration to vas deferens occlusion.

It is interesting to note the results of vas deferens occlusion reported by Sand (8). Fifteen cases of vas occlusion were reported, some having been observed one year or longer after the operation. Two cases only are reported as degenerate and thirteen in which no degeneration had occurred, yet Sand states a confirmation of Bouin and Ancel that vas ligation produces degeneration; he states, however, that often a year is not sufficiently long to wait for degeneration. Is it not time to reverse our conceptions and conclude that vas deferens ligation does not of itself produce degeneration of the testis?

The unsuspected intensity of epididymal hypertrophy is worthy of additional remarks. Spermatogenetic activity has continued without evidences of arrest after the excurrent duct of the testis has been ligated. The products resulting from this activity, if permitted to accumulate in the tubules would be expected to produce an arrest of development, perhaps of degeneration, on account of abnormal pressure. It is particularly interesting to realize that the normal currents directed outward from the testis proper to the epididymis, functioning normally for the transportation of spermatozoa, perhaps also of certain secretions, are of sufficient intensity to overcome the resistance of a filled epididymis and an internal pressure great enough to cause a doubling or tripling in size of the latter structure. The tubules, despite their activity and despite the backward pressure from the epididymis, are not filled with the products of their own activity, but these products are removed into the reservoir provided by the epididymis. Miss van Wagenen (9) has recently confirmed Steinach that ligation between the epididymis and the testis produces degeneration, perhaps through pressure atrophy; she also declares degeneration after vas deferens ligation. From our own materials, however, *vas*

deferens occlusion in rabbits does not produce degeneration up to six months after operation if the testes retain their normal scrotal relationships; Sand has shown that degeneration does not follow even after a year; Oslund failed to obtain it up to ten months; Shattock and Seligman (10) on sheep found normal testes one year after the operation; numerous clinical reports on man show normal testes several years after vas deferens occlusion; and I have shown that normal tubules are present even in testis grafts. Since a single factor or condition to be operative should express itself within a time equal to one-half the sex life of an individual animal, we should conclude, I believe, that vas deferens ligation of itself does not produce degeneration of the testis.

It will be understood that this operation, the so-called Steinach operation, is practiced on the human individual for a supposed tuning up of a wornout organism. The significance of the testis reactions following vasectomy as described by Steinach can be weighed briefly in two considerations: First, in the many cases of vasectomy performed in our laboratory on guinea pigs, rats, sheep, and rabbits no single case has ever occurred where interstitial cell hypertrophy followed as a result of this operation; and it should be remembered that this is the only morphological basis upon which Steinach's regeneration rests. Second, should an hypertrophy follow, it would remain to be proved that a mass of interstitial cells in the testis represents a corresponding quantitative intensity in the production of internal secretions.

But to return again to known facts what factors, may we ask, are the causes of the rapid and striking degeneration of the testis when it is displaced from its normal scrotal environment? I have shown above that a delicate and necessary relationship exists between a normal germinal, or tubular, epithelium and the scrotum. What are the factors operative in causing complete disorganization, within seven or eight days, and ultimate degeneration of all germinal cells when the testis is kept in the peritoneal cavity?

Having eliminated every factor that came to mind as a cause of the degeneration excepting one, I stated in 1922 (11) that a differential body temperature was suspected as the causal

factor. Taking note of a similar suggestion by Crew in the same year (12) that body temperature might be the cause of the lack of spermatozoa in undescended testes my idea was strengthened and experiments were designed to test the hypothesis. If it is a higher temperature of the body cavity that causes degeneration, then scrotal temperatures should be lower than peritoneal temperatures, and the scrotum would serve as a local thermo-regulator. It should then follow that by preventing the scrotum from functioning in this hypothetical manner the testes should degenerate while located in their normal position.

With the co-operation of Dr. Oslund the scrotum of a ram was insulated against loss of heat by securely, though loosely, encasing it in woolen materials and a water-proof covering, sewed to fit the scrotal contour, and suspended sufficiently by artificial supports as to preclude binding the scrotum or producing abnormal pressures (13). Within eighty days the testes were found to be devoid of spermotozoa; many tubules were in advanced stages of degeneration, the tubules being filled with loosened, degenerating cells similar to peritoneally retained testes, while many tubules lacked entirely the germinal epithelium. *The animal had sterilized itself with its own body heat due to prevention of the local thermo-regulatory function of the scrotum.*

With Mr. W. J. Quick, temperature readings were made with ordinary thermometers passed into the abdomen through locally anaesthetized abdominal regions of rats, rabbits, and guinea pigs (14). One thermometer bulb in the peritoneal cavity and another passed through the open inguinal canal into the scrotum, alongside the testis, showed us that at the same moment the scrotal temperature was appreciably lower than that in the peritoneal cavity in all cases. The differences between the two cavities varied as the external environmental temperature varied. Thus in a white rat observed in a room temperature of 16°C. the scrotal temperature was 8°C. lower than that of the peritoneal cavity. This gives absolute proof, therefore, that the normal environmental temperature of the testes is appreciably lower than the general body temperature.

There remained for disposal one further assumption to provide actual proof of the correctness of our working hypothesis:

the testis should undergo degeneration following the application of temperatures slightly higher than those normal for it.

It was found that hot water pads applied to the external surface of the guinea pig scrotum, raising the temperature approximately 6° to 7°C. above normal body temperature for a period of fifteen minutes resulted in severe tubular degeneration within ten days after application (15). Increasing or decreasing either the length of application or the degree of temperature applied we can produce at will any stage of degeneration desired from the destruction of a few peripheral tubules to complete degeneration of all seminiferous tubules in the testis. Direct submergence of the testis in a controlled saline bath of 47°C. for five minutes is sufficient to produce complete degeneration of every tubule of a ginuea pig testis within five days after the application. Thus the application of temperature slightly higher than its normal is shown to be fatal to the generative portion of the testis and the degeneration following such an application is very similar to the type occurring after testis elevation into the peritoneal cavity.

The totally independent work of Fukui (16), a Japanese investigator, but recently published, arrives at a similar interpretation with respect to the effects of temperature on the testis and the explanation of degeneration of testes elevated into the body cavity. Applying heat in the form of hot water, hot air, heat of the sun, and arc light heat Fukui has worked out a so-called "heat curve" of the testis in relation to time of application and degree of temperature employed. A very striking observation, however, and one that greatly strengthens our proof of degenerate testes when elevated into the body cavity was made as follows: Fukui elevated both testes of an animal into the peritoneal cavity but artificially cooled the external area on one side in the region of the elevated testis. He found that in the course of a few days the testis in the artificially cooled area was normal, whereas the uncooled testis was highly degenerated. Thus with all the accumulated evidence there should no longer be any doubt that our conception of the effects of the body temperature on the testis condition is the correct one.

Let us examine briefly, then, the qualifications of the scrotum as a local thermo-regulator for the testes. In its simple

form in the rodent the scrotal sac is but an outpouching of the peritoneal cavity posteriorly underneath an area of skin much thinner than ordinary skin, and well provided with sweat glands; the muscular layers are exceedingly thin; subcutaneous fat is absent, and the organ varies in size and shape as environmental temperatures vary. Thus on hot days the scrotum relaxes to its full pendent condition permitting the testes to be farther removed from the body, whereas in a cold atmosphere the scrotum is contracted, bringing the testes nearer to the body. It is difficult to differentiate a male from a female rat in low temperatures without close scrutiny, as the testes may be so elevated on scrotal contraction that their position is in reality abdominal; on hot days, however, the testes protrude considerably in a post-anal position. A similar adjustment follows also for man.

The physical and physiological principles of a local temperature regulator are inherent in the mechanism, and in consideration of all proofs brought forward I have no hesitancy in stating that *the scrotum of mammals is now to be considered a local thermo-regulator for the testes and that the regulatory or functional capacities are indispensable for the production of differentiated germ cells or the maintenance of those already produced.* Not longer than three years ago Cunningham, in his book Hormones and Heredity (17), stated that "Various causes have been suggested for the formation of the scrotum, but no one has ever been able to suggest a use for it" (page 147). I believe we have not only been able to suggest a use for it, but have proved its function and utility.

Objections may be raised against the idea, however, due first to the lack of such a structure in the bird, where the testes are abdominal and the body temperatures even higher than that of the mammal; and second to the lack of it in some mammals (monotremes, elephant, many aquatic forms, bats, etc.). In regard to the first objection may I not state that the bird and mammal are entirely two different animals. Many structural and physico-chemical differences exist between these two forms. Because the testicular tissue is a decidedly heat labile substance in one is no good reason for assuming it in the other; slight physico-chemical differences may produce an entirely different

reaction system, and we need not be troubled by such physiological differences, particularly when we appreciate the many structural differences between the two animals. As regards the mammal it need only be mentioned that most biologists now assume that an evolution of animal forms has occurred within the class mammalia as well as among vertebrates as a whole, or invertebrates. In the monotremes, the lower reptile-like mammals in which it is said body temperatures are by no means constant but are subject to wide variations, the testes are located in the reptilian position—namely, just posterior to the kidneys in the abdomen. As we ascend the scale of mammals a typical scrotum is gradually produced. In some mammals (bat, sloth, etc.) the testes have descended into the pelvic region and have taken up a position against the anterior abdominal wall in a pouch-like depression over which the skin is very thin. It is unquestioned that sufficient temperature adjustment is thus obtained, else we would not have such animals preserved for our edification. In rodents an onward step has been made; the testes protrude into the outpouching of the peritoneum in the inguinal region, but the final scrotal condition has not yet been accomplished as the sacs present a wide open connection capable of permitting passage of the testis into and out of the abdomen. The final closed scrotum is gained only in the higher mammals. It should not trouble us exceedingly that variations have occurred during its evolution—adaptations perhaps—for such have been present even in the evolution of such typical structures as appendages.

We may therefore assume a gradual evolution of a scrotum within the mammal group and may we not, with all justice, consider that perhaps the evolution of the entire mammalian group may have been more or less dependent upon this scrotal evolution? It involves certainly the capacity of the reproductive system to function and therefore the very foundation of the race.

While adding little actual accomplishment to solving the riddle of the internal secretion of the male gonad I believe the fundamental reactions of the testes under the varying conditions discussed, and the attempt at an explanation of the tissue reactions, will give a point of departure from which a more rational interpretation of observed facts may proceed.

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A QUANTITATIVE STUDY OF THE HUMAN HYPOPHYSIS CEREBRI, OR PITUITARY BODY*

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MINNEAPOLIS

While the general size and appearance of the normal human hypophysis is generally well known, this organ has become of such clinical importance that more accurate data are necessary especially on the limits of normal variability, not only of the organ as a whole but also of the size and histological appearance of its various parts. It may be well to recall that the pituitary body is a complex structure composed of pars anterior (pars distalis), pars nervosa (processus infundibuli or pars posterior), pars intermedia (juxtaneuralis or pars infundibularis) and pars tuberalis (an epithelial extension along the under surface of the tuber cinereum or floor of the third brain ventricle). Most of these are shown in Figure 1, as seen in horizontal section. These various portions apparently differ functionally and must, therefore, be evaluated independently.

While there are thousands of weights of the main portion of the gland as a whole, there are no accurate figures on the mass of the various subdivisions. Even the weight and dimensions of the whole organ as recorded are not so reliable as they might have been because it is not clearly indicated how much of the surrounding connective tissue (dura mater) and of the infundibular stalk is included. The stalk represents about 5% of the whole organ, but may reach 8%. The dural sheath about the hypophysis may easily be as much as 25% of the weight of the gland. In our material we have dissected off practically all the dura, leaving only the thin capsule or pial covering as shown in Figure 1. The pial sheath cannot be removed without removing with it some of the gland parenchyma. The stalk we have

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cut off as short as possible because in the ordinary autopsy only a portion is left attached to the rest of the gland and there was no means at hand for determining how much was still connected with the brain.

TECHNIQUE

The method employed in obtaining the original data here presented has already been described and published in detail (Rasmussen and Herrick, 1922). It is sufficient here merely to state that serial sections of whole undamaged normal organs

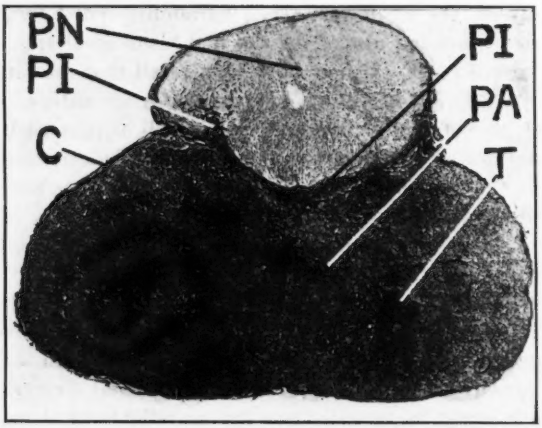

Figure 1. Photograph of a horizontal section of a typical normal human hypophysis to show the regions involved in this report as well as the amount of capsule or connective tissue left on the gland. C, Capsule; PN, Pars Nervosa; PI, Pars Intermedia; T, Trabecula; PA, Pars Anterior.

were projected at a magnification of 20 diameters (surface area magnification of 400) upon heavy paper which has a fairly constant weight per sq. cm. The various subdivisions of the gland were outlined with a fine hard pencil or ink and then cut out. The relative weight of the paper representing a given part of the organ gives the necessary data for determining the weight of that part in the fresh gland if the weight of the whole fresh gland is known and if the specific gravity of all parts is the same and the histological technique causes equal shrinkage of all parts. The differences in specific gravity are negligible for all practical purposes and the shrinkage is fairly uniform (Rasmussen and

Herrick, 1922). So if the combined weight of the pieces of paper representing, say, pars nervosa is 20% of the weight of the paper representing the whole gland and the fresh hypophysis weighed 0.5 grams, then the nervous lobe weighs 20% of 0.5 grams, which is 0.1 of a gram.

TABLE I
WEIGHT OF HUMAN HYPOPHYSIS CEREBRI

Authority	Date	No. of Cases	Age in Years	Weight in Grams				Remarks
				Male	Female	Both Sexes	Extremes	
Schœnemann	1892	9	20–46	.612			.400– .700	None normal after 50 years.
		2			.975		.600–1.35	
Bryce and Beadles	1893	50	22–78	.453		.527	.130– .712	Insane
		50	31–84		.600		.384– .896	
Comte	1898	33	22–70	Non-preg. .480			.392– .885	None normal after 50 years.
		6	21–39	End of preg. .911			.540–1.265	
Caselli	1900	50	Adult	.667				Mostly mental cases
		50	Adult		.731			
Launois	1904	50	Aver. = 50½	.588 but only .480 if cereb. hemor. is excluded				11 cases cerebral hemorrhage = .755
		50			.601			
Latreille	1908	6	44–60	.615			.350– .800	
		15	22–68		.705		.400– .950	
Archard-Loeper	1908	?	Adult			.500		
Halliburton, Candler, Sikes	1909	18	Adult	.469			4 over .500	Asylum material
		24	Adult		.567		4 under .50	
Creutzfeldt	1909	110	Various			Both sexes	.900–1.800	Increases till 30. Decreases after 50
Erdheim and Stumme	1909	92	21–70	.612			.400– .920	30–40 years = .643 (23 cases)
		13	21–50		.665 (Nullipara)		.400– .890	
		39	21–84		.745 (Unknown)		.350–1.050	
		38	21–40		.847 (Primipara)		.360–1.130	To 58 years post-partum
		73	Adult		.865 (Multipara)		.530–1.450	2-16 children

WEIGHT OF THE WHOLE HYPOPHYSIS

Table I gives a summary of the most important data found in the literature on normal or nearly normal human adults as well as our own determinations.

Some additional data were not tabulated for various reasons. Thus Parski (1901) and Testut (1912) give weights which were

excluded because they were far too low to be representative. Livon (1909) also gives a rather low average (0.442) without stating the number, sex or nature of the material. Cutore (1910) has a table of 25 weights, but only 6 of these are adult and they died of various diseases. On the other hand, Schönemann (1892) excluded many cases from his list of normals that others would

TABLE I—(Continued)
WEIGHT OF HUMAN HYPOPHYSIS CEREBRI

Authority	Date	No. of Cases	Age in Years	Weight in Grams				Remarks
				Male	Female	Both Sexes	Extremes	
Lucien	1911	100	20–85	.500-.710			.500– .710	Change after 50 is not pathological
			20–80		.570-.970		.570– .970	
Kolde	1912	3	20–34		1.113 (Just post-partum)		.740–1.700	1–5 children
Tolken	1912	38	18–70+			.540		
Munson-Shaw	1914	?	Adult			.540		
Simmonds	1914	800	16–20	.688	.701			Not certain that pregnant females were excluded
			21–30	.733*	.801			
			31–40	.741	.814			
			41–50	.687	.775			
			51–60	.666	.798			
			61–70	.660	.754			
			71–80	.697	.730			
			81–90	.599	.755			
Rœssle	1919	132	Soldiers	.627				.712 if stature is 175 cm. and over
Petersilie	1920	189	Soldiers	.621			.300– .900	
Krieger	1920	30	Adult	.580				
Rasmussen	1923	50	19–65	.560			.400– .855	Stalk and dura removed

have included. He selected only 11 out of 89 adults as being absolutely normal, considering no hypophysis normal after 50 years of age. Seventy-eight of the 89 were excluded by Schönemann for one or the other of the following four reasons: chromophilic changes in the chief cells (30 cases), overgrowth of connective tissue in the stroma of the anterior lobe (32 cases), blood vessels too abundant (9 cases), too much colloid (7 cases). Incidentally, it may be noted that the figures so often quoted from Schönemann as representing the average adult weight in reality include many children hypophyses. In order to avoid errors of

this kind, the original publications have been consulted in every case except two.

Many measurements of the three diameters accompany the weight of the organ, but since it is the bulk of the tissue that we are primarily interested in and not its exact shape, these measurements have not been included for consideration. In passing, it may be noted that the average hypophysis of about 0.6 grams in weight is in the neighborhood of 13 mm. in transverse diameter, 10 mm. in sagittal diameter and 6 mm. in vertical diameter (see e.g. Erdheim and Stumme, 1909; Tölken, 1912; Thom, 1901; Zander, 1896).

(a) SEX DIFFERENCES

It will be noticed in Table I that when the sexes are separated, the female hypophysis is noticeably heavier than the male. This difference is slight in nullipara (Erdheim and Stumme). In pregnant females and in women who have borne children the hypophysis may be expected to be distinctly larger (Comte, 1898; Erdheim and Stumme, 1909; Kolde, 1912). Thoan (1907) and others have similarly recorded this difference during pregnancy. Erdheim and Stumme plotted a curve which shows that there is an increase in hypophyseal weight to the 10th lunar month of pregnancy and then a rapid decline. Their data, as well as some other incidental observations, indicate also that repeated pregnancies result in a still larger hypophysis in many cases. If the 72 cases discarded as normals by Schönemann (1892) (for doubtful reasons as already explained) be separated according to sex, the 41 male hypophyses averaged 0.710 grams as compared with 0.745 grams for 31 females.

The average for our series of 50 perfect hypophyses from adult males, who met sudden accidental death in most cases, is somewhat lower than the figures given by others. This may be due to the fact that we remove the dural covering, leaving only the thin capsule of pia mater, and cut off the infundibular stalk before the weight is taken. This seems the only logical procedure with ordinary autopsy material. As already explained, the method of dissecting out the gland may then make as much as 33% difference in the weight. For this reason it is not justifiable to combine the data given by the different writers, since they are

not specific enough as to what is included and what is excluded.

We have not been able to get enough normal female hypophyses to check carefully with the male series.

(b) AGE DIFFERENCES

The extensive data given by Simmonds (1914), particularly, indicate that the hypophysis is largest from 20 to 40 years of age and that in the male it tends to decrease markedly in old age. Also in our own data, as shown in Table VI, the group between 35 and 45 years of age has the highest average weight, while the oldest group (46-62 yrs.) has the smallest average weight. This is not due to a difference in stature, for the group with the highest weight incidentally happens to have the smallest average stature, which would tend to annul the age differences, as will be seen from what follows.

(c) RELATION OF HYPOPHYSEAL WEIGHT TO STATURE

The principal figures relating to stature have been collected in Table II.

TABLE II

RELATION OF WEIGHT OF HYPOPHYSIS TO STATURE

Authority	No. of Cases	Stature (cm.)	Weight of Hypophysis (grams)	Remarks
Rœssle	?	175 and up	.712	As compared with .627 when all heights (132 soldiers) are included
Petersilie	13	Under 160	.566	Total cases 185 soldiers.
	36	161–165	.580	
	61	166–170	.646	
	53	171–175	.632	
	14	176–180	.718	
	8	181–185	.723	
Rasmussen	10	159–173	.537	20–45 years of age.
	10	173–192	.652	

This is interesting because of the influence of the functional activity of the hypophysis to giantism. In general this organ may be expected to be larger in tall than in short men. It has been repeatedly shown that no such correlation exists between adult body weight and weight of the hypophysis. Since the hypophysis of old men tends to decrease distinctly in size, we eliminated from our cases all those above 45 years so as to have more uniform material, and then divided them into two equal

groups according to stature (see Table II). The ones with statures below 173 cm. had a distinctly lower average hypophyseal weight than the other group with statures above 173 cm.

(d) RELATION OF THE WEIGHT OF THE HYPOPHYSIS TO THE SIZE OF THE SELLA TURCICA

From numerous studies on the fossa hypophyses (Zander, 1896; Fitzgerald, 1910; Gibson, 1912; Cope, 1916; Johnston, 1917; Jaugeas, 1918; Howe, 1919; Jewett, 1920; Enfield, 1922; Mintz, 1922; Gordon and Bell, 1922; Camp, 1923; Knox, 1923),

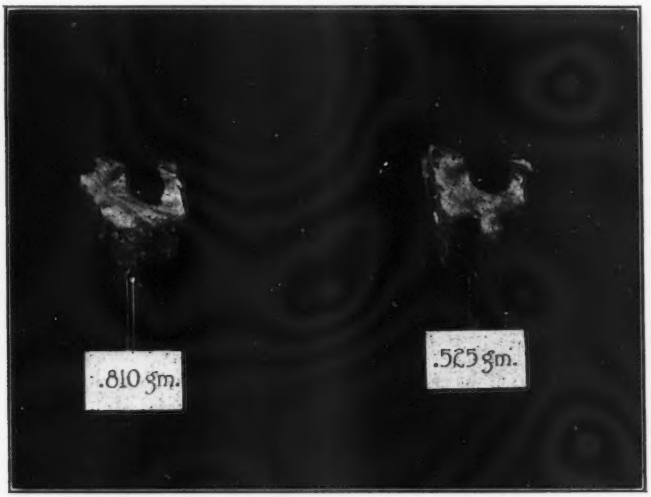

Figure 2. Photograph of two normal hypophyseal fossae with the weight of the hypophysis taken from each to show the discrepancy that may exist between the size of the sella and the hypophysis.

it is evident that it varies greatly in size and shape in normal individuals. Since the hypophysis was frequently received in situ with the sella intact, it was incidentally noticed that there may be a wide variation between the bony compartment and the weight of the inclosed hypophysis—a fact which has already been fully appreciated by some clinicians (e. g., Timme, 1919). There are still those, however, who are prone to stress too much the importance of the size of the sella. A good illustration of

the discrepancy which may exist is shown in Figure 2, which is a photograph of two normal sellae, but slightly under average dimension, with the weight of the corresponding hypophysis attached. Although the cubical space in these two sellae is almost the same, the hypophysis in one (0.810 grams) was 50% larger than the hypophysis in the other (0.525 grams). In fact, an x-ray picture of the one containing the larger hypophysis would have given no suggestion that the hypophysis was extreme in size for a normal male. The amount of surrounding connective

TABLE III

WEIGHT OF PARTS OF HUMAN HYPOPHYSIS
MALE—ADULT 20-34 YEARS OF AGE

Autopsy No.			20-276	20-408	20-372	20-252	20-279	20-44	22-205	20-446	22-327	22-80
Age			20	22	24	25	29	31	31	32	32	34
Pars Ant. (Dist.)	Trab.	G.	.0020	.0007	.0005	.0020	.0015	.0050	.0022	.0036	.0017	.0011
		%	.32	.14	.09	.34	.36	1.06	.30	.76	.28	.17
	Paren.	G.	.4266	.4024	.4253	.3989	.3274	.3460	.5683	.3473	.4302	.5330
		%	69.37	79.52	75.40	69.95	79.28	73.62	76.28	72.36	71.70	84.33
	Total	G.	.4286	.4031	.4258	.4007	.3299	.3510	.5705	.3509	.4319	.5341
		%	69.69	79.66	75.49	70.29	79.64	74.68	76.58	73.12	71.98	84.50
Pars Nerv. (Proc. Infun.)		G.	.1042	.0367	.1109	.1219	.0516	.1000	.0525	.0876	.1436	.0743
		%	16.95	7.25	19.66	21.39	12.51	21.28	7.05	18.25	23.94	11.75
Pars Inter. (Juxt.)	Colloid	G.	.0338	.0511	.0022	.0029	.0150	.0030	.0060	.0002	.0011	.0035
		%	5.50	10.10	.39	.50	3.63	.64	.80	.05	.18	.55
	Paren.	G.	.0022	.0008	.0017	.0014	.0028	.0041	.0036	.0014	.0039	.0075
		%	.35	.17	.31	.24	.67	.87	.48	.30	.65	1.19
	Total	G.	.0360	.0519	.0039	.0043	.0178	.0071	.0096	.0016	.0050	.0110
		%	5.85	10.27	.70	.74	4.30	1.51	1.28	.35	.83	1.74
Capsule		G.	.0462	.0143	.0234	.0432	.0147	.0119	.1124	.0397	.0195	.0127
		%	7.51	2.82	4.15	7.58	3.56	2.53	15.09	8.28	3.25	2.01
Whole Gland		G.	.615	.506	.564	.570	.413	.470	.745	.480	.600	.632
Stature		(cm.)	175	162	182	173	170	181	189	160	173	192

tissue and above all the capacity of the intercavernous sinus vary greatly and account for the difference between the size of sella turcica and hypophysis. For these meningeal relations of the hypophysis consult Koller (1922), Hughson (1922) and Cowdry (1922).

THE VOLUME OF THE CHIEF SUBDIVISIONS OF THE HYPOPHYSIS

Only general statements regarding the proportion of the various parts of the human hypophysis have been found in the literature. The outside measurements of the anterior lobe and the posterior lobe that have been published give no adequate or accurate idea of volumes. In Tables III, IV and V are recorded our findings in thirty selected cases. The autopsy numbers refer to the files of the Department of Pathology, University of Minnesota. The three age groups are compared in Table VI.

TABLE IV
WEIGHT OF PARTS OF HUMAN HYPOPHYSIS
MALE—ADULT 35-45 YEARS OF AGE

Autopsy No.			22-295	22-329	22-332	20-323	20-291	20-380	22-344	22-218	21-280	22-266
Age in Years			35	35	35	36	36	37	40	40	43	45
Pars. Ant. (Dist.)	Trab.	G.	.0012	.0018	.0026	.0043	.0010	.0032	.0008	.0014	.0016	.0063
		%	.15	.26	.33	.84	.24	.49	.15	.29	.26	.74
	Paren.	G.	.5435	.4744	.5379	.3832	.332	.4501	.4113	.2824	.4048	.6045
		%	70.58	68.45	72.21	72.30	76.87	68.20	78.36	59.46	66.36	70.70
	Total	G.	.5447	.4762	.5405	.3875	.3338	.4533	.4121	.2838	.4064	.6108
		%	70.73	68.71	72.54	73.14	77.11	68.69	78.51	59.75	66.62	71.44
Pars Nerv. (Proc. Infun.)		G.	.1150	.1667	.1522	.1120	.0816	.1538	.0750	.1366	.1458	.1371
		%	14.94	24.05	20.43	21.13	18.84	23.30	14.30	28.76	23.9	16.03
Pars Inter. (Juxt.)	Colloid	G.	.0019	.0064	.0025	.0046	.0032	.0022	.0039	.0033	.0032	.0074
		%	.25	.92	.34	.86	.74	.33	.74	.70	.53	.87
	Paren.	G.	.0013	.0032	.0076	.0022	.0045	.0110	.0034	.0024	.0201	.0188
		%	.17	.46	1.02	.42	1.03	1.67	.64	.51	3.29	2.20
	Total	G.	.0032	.0096	.0101	.0068	.0077	.0132	.0073	.0057	.0233	.0262
		%	.42	1.38	1.36	1.28	1.77	2.00	1.38	1.21	2.82	3.07
Capsule		G.	.1070	.0406	.0422	.0234	.0099	.0389	.0306	.0489	.0345	.0809
		%	13.90	5.86	5.67	4.42	2.28	5.90	5.82	10.28	5.66	9.46
Total Weight		G.	.770	.693	.745	.530	.433	.660	.525	.475	.610	.855
Stature		(cm.)	174	160	170	171	160	174	168	159	180	175

From Table VI it will be seen that the pars anterior represents about 72% of the total organ, pars nervosa 18%, pars intermedia 2%, and the capsule 8%. The amount of capsule varies somewhat with the ability to dissect away the dura. In some cases, especially in older individuals, it tends to adhere to the posterior surface. In general it cannot be completely removed from the interlobular sulcus without danger of tearing

the lobes apart. The table indicates that the capsule is thicker in the oldest group. The difference is too much to be entirely accounted for by dissecting technique. Others have also noted that there is an increase in the connective tissue with advancing years.

TABLE V

WEIGHT OF PARTS OF HUMAN HYPOPHYSIS
MALE—ADULT 46-62 YEARS OF AGE

Autopsy No.			22-150	21-68	22-190	22-290	20-433	20-429	21-66	22-282	20-465	22-227
Age			(?)	50(?)	52	55	57	58	58	59	60	62
Pars Ant. (Dist.)	Trab.	G.	.0014	.0099	.0006	.0012	.0018	.0019	.0072	.0013	.0025	.0016
		%	.25	1.70	.16	.24	.43	.36	1.71	.22	.48	.34
	Paren.	G.	.3675	.3743	.3513	.3912	.2833	.3524	.2859	.3262	.4395	.2224
		%	66.82	63.99	86.73	77.61	69.11	67.76	68.08	55.29	84.35	46.04
	Total	G.	.3689	.3843	.3519	.3924	.2851	.3543	.2931	.3275	.4420	.2240
		%	67.07	65.69	86.89	77.91	69.54	68.12	69.79	55.51	84.83	46.38
Pars Nerv. (Proc. Infun.)		G.	.1054	.1319	.0271	.0625	.1015	.0929	.0722	.1329	.0597	.1466
		%	19.16	22.54	6.70	12.40	24.77	17.87	17.20	22.53	11.46	30.36
Pars Inter. (Juxt.)	Colloid	G.	.0069	.0055	.0015	.0025	.0025	.0054	.0036	.0011	.0007	.0052
		%	1.25	.94	.36	.39	.61	1.04	.86	.19	.13	1.08
	Paren.	G.	.0023	.0104	.0019	.0010	.0005	.0057	.0040	.0112	.0082	.0056
		%	.42	1.77	.47	.20	.13	1.10	.95	1.89	1.58	1.16
	Total	G.	.0092	.0159	.0034	.0035	.0030	.0111	.0076	.0123	.0089	.0108
		%	1.67	2.71	.83	.59	.74	2.14	1.81	2.08	1.71	2.24
Capsule		G.	.0667	.0529	.0225	.0462	.0203	.0617	.0471	.1173	.0105	.1016
		%	12.12	9.05	5.56	9.16	4.95	11.87	11.21	19.88	2.01	21.03
Whole Gland		G.	.550	.585	.405	.504	.410	.520	.420	.590	.521	.483
Stature		(cm.)	173	169	179	165	171	170	163	169	170	170

(a) PARS ANTERIOR

Under the heading of parenchyma is included the usual epithelial structures and ordinary vascular stroma, but not the two connective tissue trabeculae which carry the larger blood vessels into the lobe (Figures 1 and 3). These trabeculae seemed to vary enough (0.0005-0.0099 grams) to warrant their separation from the rest of the lobe, although they constitute only a fraction of one per cent of the whole organ. Pars anterior seems to constitute a larger percentage of the hypophysis in young adults than in older individuals. The greatest variability occurs in the oldest group where the extremes (48.38% to 86.89%) are

encountered. The absolute weight in all the 30 cases varies from 0.2240 grams to 0.6108 grams.

(b) PARS NERVOSA

This portion seems relatively smallest in the youngest group. This, as will be noted below, is mostly due to the large masses of colloid (Fig. 3) met with in several of the young adults, the colloid having apparently encroached upon the posterior lobe. The variability (0.0271 grams to 0.1667 grams) is still greater than in pars anterior.

TABLE VI

COMPARISON OF THE WEIGHT OF THE PARTS OF THE HUMAN HYPOPHYSIS FOR THE THREE AGE GROUPS

			20–34	35–45	46–62	Extremes (All 30 Cases)	Average 30 Cases	All Cases in Round Numbers
Pars Anterior (Distalis)	Trabeculae	G.	.0020	.0025	.0029	.0005— .0099	.0025	
		%	.38	.38	.59	.14 — 1.71	.45	
	Parenchyma	G.	.4206	.4425	.3394	.2224— .6045	.4008	
		%	75.18	70.32	68.58	46.04 —86.73	71.36	
	Total	G.	.4226	.4450	.3423	.2240— .6108	.4033	
		%	75.56	70.70	69.17	46.38 —86.89	71.81	72
Pars Nervosa (Proc. Infun.)		G.	.0883	.1276	.0933	.0271— .1667	.1031	
		%	16.00	20.60	18.50	6.70 —30.36	18.37	18
Pars Intermedia (Juxtaneuralis)	Colloid	G.	.0119	.0038	.0035	.0002— .0511	.0064	
		%	2.23	.63	.69	.05 —10.10	1.18	1
	Parenchyma	G.	.0029	.0076	.0051	.0005— .0201	.0052	
		%	.52	1.14	.97	.13 — 3.29	.88	1
	Total	G.	.0119	.0114	.0086	.0016— .0519	.0116	
		%	2.76	1.77	1.66	.35 —10.27	2.06	2
Capsule		G.	.0338	.0456	.0547	.0099— .1173	.0447	
		%	5.68	6.93	10.68	2.01 —19.88	7.76	8
Average Weight of Whole Gland		G.	.560	.630	.499	.405 — .855	.563	
Stature		(cm.)	176	169	170	159—192	172	

(c) PARS INTERMEDIA

This is the smallest of the three chief divisions of the organ and also the most variable. Since there may be large masses of colloid in or closely associated with this region, it has been separated into parenchyma and colloid. It is not clear in all in-

stances that a particular colloid mass is actually in the intermediate portion; but since it is usually impossible to exclude this possibility it was thought best to include the doubtful colloid masses with pars intermedia. The colloid in the residual lumen (between pars intermedia and pars anterior) is also included. The globules of colloid found distinctly in pars anterior are in general too small to be seen with the magnification employed and have, therefore, not been considered. Their combined volume would not influence the values significantly.

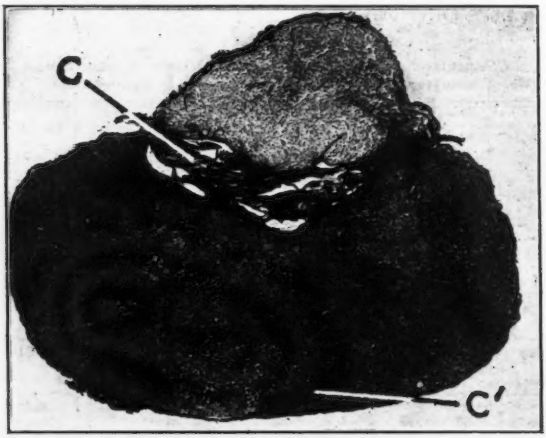

Figure 3. Photograph of a horizontal section of a normal male hypophysis containing an unusually large amount of colloid. Autopsy 20-276. C, Colloid which tends to chip in cutting, one piece (C') having been carried away out of place.

The first two cases listed in Table III had an enormous amount of colloid. In No. 20-408 it amounted to over 10% of the entire hypophysis and more than pars nervosa, and yet these were apparently perfectly normal men. Figure 3 shows a photograph of a section of the hypophysis of No. 20-276, in which over 5% of the entire hypophysis is colloid.

When it comes to the parenchyma of pars intermedia, only an approximation of its volume is claimed, because the cells are frequently irregularly scattered about in pars nervosa (Fig. 1). Greater accuracy could be obtained by using a much higher magnification so that even a single cell could be outlined. This would, however, increase the amount of work all out of propor-

tion to the returns. As Tables III, IV and V show, the weight of the parenchyma of pars intermedia varies so much relatively that nothing is gained by an extended discussion of so short a series of cases.

In connection with the discussion that is going on about the functional significance of this part of the gland, attention may be called to the fact that if it were rounded up it would make a sphere only about 2 mm. in diameter weighing only 0.005 grams in an average adult man.

TABLE VII

THREE CASES OF NON-NEOPLASTIC POST-ADOLESCENT HYPOPITUITARISM COMPARED WITH 30 NORMALS

Autopsy No.			22-368	22-246	22-81	Average of 3 Cases	Average of 30 Normals
Age			36 Years	58 Years	59 Years		
Weight			250 Lbs.	223 Lbs.	330 Lbs.		
Pars Anterior	Trabeculae	G.	.0023	.0021	.0022	.0022	.0025
		%	.42	.40	.34	.39	.45
	Parenchyma	G.	.3927	.3397	.4678	.4001	.4008
		%	70.75	64.09	75.45	70.10	71.36
	Total	G.	.3950	.3418	.4700	.4023	.4033
		%	71.17	64.49	75.79	70.48	71.81
Pars Nervosa		G.	.1076	.0882	.0939	.0966	.1031
		%	19.38	16.64	15.15	17.06	18.37
Pars Intermedia	Colloid	G.	.0027	.0010	.0101	.0046	.0064
		%	.48	.18	1.63	.76	1.18
	Parenchyma	G.	.0017	.0053	.0074	.0048	.0052
		%	.30	1.00	1.20	.83	.88
	Total	G.	.0043	.0062	.0175	.0093	.0116
		%	.78	1.17	2.83	1.59	2.06
Capsule		G.	.0481	.0938	.0386	.0602	.0447
		%	8.66	17.70	6.22	10.86	7.76
Weight of Whole Gland		G.	.555	.530	.620	.568	.563
Stature		(cm.)	173	178	189	180	172

THE HYPOPHYSIS IN POSTADOLESCENT HYPOPITUITARISM OF BOTH LOBES

Table VII gives the results of an analysis of three additional cases which had the typical physical features of so-called non-neoplastic bilobar postadolescent hypopituitarism, according to the classification of Engelbach (1920) and Tierney (1923).

An examination of the weight of the whole organ and of the various parts shows that all three cases are well within normal limits; in fact, they are very close to the average. In other words, there is nothing in the size of the hypophysis to account for the abnormal physical features of the body. In all probability anatomical studies will have to be carried into the finest cytology before many of the disorders attributed to the hypophysis can be verified by establishing a definite pathology. This work is, in fact, being extended in this direction.

DIFFERENTIAL COUNT OF THE THREE TYPES OF CELLS IN PARS ANTERIOR

One of the lines of more minute study which we have in progress is a differential count of the types of cells in pars anterior based on 100 to 200 sample areas from different regions of the lobe and involving in each hypophysis the counting of 10,000 to 25,000 cells. While not enough cases have been completed at the time this report is given, the ten normals for which figures are available indicate that about 50% are chromophobes or chief cells (varied from 37% to 64%), 35% acidophiles (varied from 23% to 43%) and 15% basophiles (varied from 9% to 27%). When a large number have been completed this phase of the work will be published in detail; but this preliminary announcement gives a rough idea of what to expect in the apparently normal male adult hypophysis.

We wish to thank Dr. E. T. Bell, Dr. B. J. Clawson, Dr. J. S. McCartney and Dr. W. A. O'Brien of the Department of Pathology, University of Minnesota, for their co-operation and the labor involved in obtaining the hypophyses in an undamaged condition.

To Miss Ruth Herrick is due the credit for much preliminary work in establishing a routine method and for the volumetric determination of six of the thirty-three cases involved in this report.

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CONCLUSIONS BASED ON A STUDY OF FOUR THOUSAND CASES OF GOITER*

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The material on which the conclusions in this paper are based consists of four thousand surgical and non-surgical cases of goiter which I have observed during the past five years at the Jackson Clinic and as a Fellow in Goiter Surgery at the Mayo Clinic. Although these observations are for the most part not new, they are culled from a great mass of facts and for the first time formulated in brief statements.

Advanced cases of exophthalmic goiter are at times treated as endocarditis by heart specialists, as nervous dyspepsia by gastroenterologists, and as neurosis by neurologists.

Little discrimination is made between cases of adenoma of the thyroid with hyperthyroidism and exophthalmic goiter. They are all too generally called "toxic goiter."

The study of goiter is complex, and much confusion exists over the diagnosis and treatment of the various forms. To bring order out of this chaos of opinion, a simple classification is essential, for example:

1. Colloid goiter.
2. Adenoma.
   (a) With hyperthyroidism (toxic adenoma).
   (b) Without hyperthyroidism (simple adenoma).
3. Exophthalmic goiter (Basedow's or Graves' disease).
4. Tuberculosis, malignancy, syphilis, thyroiditis, actinomycosis, and so forth.

The usual text book classification of goiter is confusing. The various clinical types of cystic, calcareous, and hemorrhagic goiter are merely degenerative forms of adenoma.

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COLLOID GOITER

Colloid goiters appearing at puberty are seen in 60 per cent of girls between the ages of sixteen and twenty in the goiter district of the Middle West.

Factors in the etiology of colloid goiters are: A deficiency of iodine in the soil and consequently in the drinking water; an excessive demand upon the thyroid gland for thyroxin by the muscular, osseous, and especially the reproductive systems at puberty; an undue mental and physical strain imposed upon the thyroid by modern scholastic requirements and social obligations.

The ordinary colloid goiter with its soft globular feel and symmetrical enlargement is easily diagnosed. The vascular type with thrills and bruits, pseudo-exophthalmos, tachycardia, and nervousness must be differentiated from exophthalmic goiter by the absence of true exophthalmos, quadriceps loss, or severe loss in weight. A normal basal metabolic rate confirms the diagnosis of colloid goiter.

In the treatment of colloid goiter, three common mistakes are:

1. The diagnosis is too long delayed and treatment is begun too late.
2. There is no uniformity in the method of treatment.
3. Treatment is continued in spite of the development of large adenomas.

Colloid goiter may be prevented by administering 10 mg. of sodium iodide once a week during the school year, as proved by Marine and Kimball.

The treatment of colloid goiter should be begun early, since adenomas tend to develop between the ages of sixteen and twenty.

The vascular type of colloid goiter responds most favorably to thyroid extract or thyroxin. Iodine gives better results in the ordinary type.

Apparently adenomas develop in neglected colloid goiters as a form of compensatory development. Consequently the incidence of adenoma of the thyroid is decreased by the prophylactic treatment of colloid goiter.

ADENOMAS OF THE THYROID

Adenomas rarely cause symptoms of hyperthyroidism before the age of twenty-five, unless provoked by iodine medication.

One in every four adenomas becomes toxic before the patient reaches fifty years of age.

One in every five adenomas develops a substernal projection.

Five women have adenomatous thyroids to every man that has one.

An adenoma is present an average of sixteen years before the onset of toxic symptoms.

The onset of toxic symptoms is both more gradual and insidious in adenoma than in exophthalmic goiter. Toxic symptoms exist an average of four years before the patient with an adenomatous goiter consults a surgeon.

The slowly progressive hyperthyroidism of an adenoma causes permanent and serious damage to the heart and kidneys. Myocardial degeneration, as evidenced by irregularities in heart rhythm and edema of the ankles, is of frequent occurrence.

The popular interest which has been aroused in the treat- of goiter by iodine has greatly increased the number of cases of iodine hyperthyroidism. Iodine is a specific in the prevention and cure of colloid goiter of adolescence, providing no adenomas are present. If in doubt of the presence of an adenoma of the thyroid, do not give iodine.

Thyroidectomy is indicated in the majority of patients more than twenty-three years of age with adenomas of the thyroid.

In adenoma of the thyroid the gland is asymmetrically enlarged, and one or more nodular tumors may be palpated. In exophthalmic goiter the gland is symmetrically enlarged.

In toxic adenoma acute crises do not occur. Thrills and bruits are rare. Exophthalmos is not seen. The average age of the patient is forty-four years. Hypertension and a disproportionately high diastolic pressure is the rule. The basal metabolic rate averages plus 38 per cent. Loss in weight and strength, tremor, nervousness, a moist skin, tachycardia, and palpitation occur as in exophthalmic goiter.

INTRATHORACIC AND SUBSTERNAL GOITER

An intrathoracic goiter is one in which the greater part of the enlargement of the thyroid is situated within the thorax. A substernal goiter is one in which there is a projection of only part of the thyroid into the chest. An exophthalmic goiter is never totally intrathoracic.

A history of a gradually disappearing goiter, chronic cough, choking spells, difficulty in swallowing, and increasing huskiness of the voice is indicative of a substernal or intrathoracic goiter. One patient in every four has toxic symptoms. Dilated veins on the chest occur in 10 per cent of the cases.

CARCINOMA OF THE THYROID

In one series of 100 patients with goiter observed at the Jackson Clinic during 1923, there were four cases of carcinoma. Three of the patients are now dead.

The mortality in clinically diagnosed cases of malignancy of the thyroid is 100 per cent. Is there any justification for delaying operation until a clinical diagnosis of malignancy or myocarditis can be made in adenoma of the thyroid?

Malignancy does not occur in cases of exophthalmic goiter.

An adenoma is a neoplasm; it is potentially a precursor of cancer and should be removed no matter in what part of the body it is located.

EXOPHTHALMIC GOITER

Unlike toxic adenoma, the onset of hyperthyroidism in exophthalmic goiter is acute, the average duration of symptoms being nine months. The disease is more common in youth, the average age being twenty-six years, but it may also affect children or the aged.

Exophthalmic goiter progresses by acute exacerbations and periods of remission. At the crests of the waves of hyperthyroidism all symptoms are intensified and gastrointestinal crises occur. Thrills and bruits occur in 80 per cent of the cases. Bilateral exophthalmos is observed in one of every two patients within three months of onset of symptoms.

The pulse pressure is high, a low diastolic pressure being a very important diagnostic point.

Loss in weight, in some cases rapid and extreme, is accompanied by a variable and at times excessive appetite.

Muscular asthenia is most marked in the quadriceps group of muscles.

The basal metabolic rate is not an index of the patient's ability to undergo operation, but as a diagnostic aid and a postoperative proof of the result it is invaluable. The average basal metabolic rate is plus 54 per cent.

Contrary to a generally accepted view, fever is present only during a crisis, hence there should be no difficulty in eliminating the diagnosis of tuberculosis.

PREOPERATIVE MEASURES

An examination of the vocal cords should be made in every case of adenoma of the thyroid. Laryngeal examination will show partial or complete paralysis of one or both cords in one in every fifteen cases. This evidence may prove important from a medico-legal standpoint postoperatively. If one cord is paralyzed before operation, especial care must be taken not to injure the nerve supply of the other cord.

A roentgen ray examination of the chest is of value in eliminating substernal or intrathoracic goiters.

The two most important preoperative measures are the choice and the time of operation. A severe recent loss in weight and strength with a rapidly rising metabolic rate warns of an approaching crisis. If possible, operation should be performed during a remission or early in the course of the disease when the weight is stationary or increasing.

Two cubic centimeters of tincture of digitalis is given to all patients three times a day for three days as a minimum.

As patients grow weak from lying in bed, they should be allowed to be up from one to three hours daily.

Thirty grains of bromides daily quiets patients with toxic goiter.

A diet of 4,000 calories a day is required as a minimum to maintain body weight.

In exophthalmic goiter Lugol's solution reduces the metabolic rate an average of 20 per cent preoperatively. There is a proportionate clinical improvement, and the necessity for ligation is obviated in 75 per cent of the cases.

Lugol's solution and ligation are not indicated in the treatment of toxic adenoma.

I give two hypodermics before all operations, gr. ¼ of morphine, followed in fifteen minutes by gr. 1/300 of scopolamin.

ANAESTHESIA

Because of the numerous advantages of the novocain method of local anaesthesia, I use it in 90 per cent of cases.

The operator and his assistants must handle the tissues most gently and carefully to minimize the sensation of pain and pressure.

Any trauma or injury to the recurrent laryngeal nerve may at once be detected by talking with the patient.

When the operation is finished, undetected bleeders may be found by causing the patient to cough and strain.

The disagreeable postoperative nausea and vomiting following ether narcosis are eliminated.

The risk of postoperative hyperthyroidism is diminished.

There is a decreased chance of postoperative aspiration pneumonia, although pneumonia may occur.

The operator can tell whether the patient's condition warrants continuing the operation.

The disadvantages of novocain anaesthesia are:

Increased strain on the surgeon.

Increased psychic disturbance to the patient.

Increased time required for operating.

OPERATION

Team work, rather than individual brilliancy on the part of the surgeons, favors a rapid, bloodless resection of the thyroid gland.

Time may be gained by preventing hemorrhage from the small vessels in dissecting up the skin and platysma, by applying a very sharp scalpel edgewise and not too deep, while strong traction is exerted by assistants on either side of the flap.

Opinions differ on the necessity of dividing the sternohyoid and sternothyroid muscles. Unquestionably it gives better exposure, and whenever this is required as in the case of a vascular, friable exophthalmic goiter or a large colloid adenoma, there should be no hesitation about dividing the muscles.

Early exposure and anaesthetizing of the upper poles, followed by double clamping and dividing, permits better mobilization of the gland, reduces the factors of shock and pain, and decreases hemorrhage.

Having properly exposed the goiter by dissecting with the scalpel along the plane of cleavage, one should ligate the lateral veins in order that these vessels may not be torn away and retracted into the wound.

The recurrent laryngeal nerve must be avoided by placing clamps parallel and not at right angles to it. Only the edges of the capsule or the surface of the gland are sutured.

POSTOPERATIVE CARE

Postoperative patients must be kept under the influence of morphine for from twenty-four to forty-eight hours, depending on the degree of toxicity. Fluid intake must be kept up to 3500 c.c. Digitalin, gr. 1/25 hypodermically, may be given every hour if indicated.

Eighty-five per cent of the cases of toxic goiter are cured by surgery. Medical measures may temporarily benefit but only delay the relief possible to obtain by surgery. Roentgen ray and radium are contra-indicated in the treatment of any type of goiter except exophthalmic goiter. In these cases treatment must be continued over a long period of time with only uncertain results.

HETEROACTIVITY OF THE PITUITARY GLAND WITH HYPERTHYROIDISM. DISCUSSION OF THE SYNDROME AND REPORT OF AN ILLUSTRATIVE CASE.

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INTRODUCTION

The great divergence of opinion regarding clinical classifications of diseases of the pituitary gland, is largely responsible for the confusion existing in the literature. Some few writers still retain the original classification advanced by Cushing, others, with a somewhat commendable but hardly progressive conservatism, are still willing to admit only such outstanding syndromes as gigantism, acromegaly and dystrophia adiposogenitalis to the category of definitely classified pituitary disorders, and place all other manifestations under the general nebulous heading of dyspituitarism. In addition to this barrier we are further handicapped by finding many reported cases in which the histories and data are too meager to permit reclassification.

The anatomico-physiological classification of Engelbach and Tierney (1) is not only well in accord with established experimental data, but has been elaborated by the evidence gained from a careful clinical study of over 200 cases of pituitary disorder. While it must be admitted that this classification will undoubtedly undergo changes as our knowledge on the subject increases, it now forms the best working basis for the further study of these cases. As their classification is to be utilized in the presentation of this case, it seems advisable to give a brief outline of it, at least in so far as it is pertinent to the features of this case.[1] They consider that the two lobes of the pituitary gland have certain well defined and separate functions, the anterior lobe mainly governing skeletal growth, development and

1. No attempt is made to outline the whole classification.

function of the sexual organs and the development of the secondary sex characteristics. The posterior lobe chiefly affects body metabolism. Either one or both of these lobes may become hypo- or hyper-active, or one may be in a hyper-secretory state while the other is under functioning (heteroactivity). The clinical syndrome produced depends largely on whether this altered function takes place before or after the completion of skeletal growth, especially in anterior lobe disorders.

Preadult hyperactivity of the anterior lobe gives rise to an individual with increased skeletal growth or even a giant. Gigantism, however, is not necessarily a result; the individual may simply be large and well proportioned. While this overgrowth affects all bones, it may not affect them equally, so that Engelbach and Tierney recognize three types of stature, i. e., the *normal,* in which the length of the torso is equal to the length of the lower extremities and the span of the arms equal to the height; the *acromegalic type,* in which the torso is longer than the lower measurement and the span less than the height, and in which other signs of acromegaly (slight prognathism, etc.) may be present; the *eunuchoid type,* in which the lower measurement is greater than the torso and the span greater than the height—all three types simply depending on whether the long bones of the extremities have grown the same, more or less than the short and acral bones (vertebra and facial bones).

In the *normal type* (exemplified by the present case) the head is large but in proportion to the body, and the features are well balanced. The hands and feet, while large, are also well proportioned, and radiographs show slight mushrooming of the terminal phalanges. The genitalia and sex glands are normally or even over-developed, and the sex functions, libido, potentia and menstruation are normal as long as the hyperfunction is maintained, but are totally or partially lost if the function changes to under activity.

The posterior lobe has little or no effect on skeletal growth so that we may find signs of its disorders in a person of any of the above types. Since hypofunction of the posterior lobe gives rise to a more definite chain of events than hyperfunction, and is considered to be the cause of the cardinal symptoms in this case, only this phase of its altered function will be considered.

In pure posterior lobe hypofunction, uncomplicated by any other endocrine disorder, the disturbances are mainly metabolic and include the following: low basal metabolism,[2] increased carbohydrate tolerance, low blood pressure, subnormal temperature, slow pulse, atonic constipation, girdle and mammillary adisposity, great fatigability, general malaise, headaches, and, at times, anomalies in the secretion of urine (diabetes insipidus). As in other diseases we do not expect to find all of these signs and symptoms present in every case, and it must also be remembered that other endocrine glands may become secondarily involved and greatly complicate the picture.

It is very important from the standpoint of diagnosis to emphasize two rather well-known facts. *First,* those cases which begin as a hyperfunction, especially of the anterior lobe, either before or after adult life, have a remarkable tendency to later pass into a state of hypofunction, which may involve either the anterior or posterior lobe alone or in combination; so that the signs of acromegaly or gigantism may be accompanied by every feature of hypofunction, and it is only by a careful analysis of the altered functions and by correlating their presence with the physiology of each lobe that a correct diagnosis can be made. *Second,* definite alterations in the shape and size of the sella turcica are found only in those cases where a pituitary neoplasm is responsible for the altered function. A possible exception to this statement will be referred to later.

THE CASE

Miss F. R. Single. American. Age 21. The patient was formerly employed as a stenographer, but has recently been unable to work for any length of time because of her condition. She was first seen by the writer July 21, 1922, at the Out-Patient Dispensary of the Barnes and Jewish Hospitals, and was sent from here to the Jewish Hospital for observation.

Chief Complaints were: (1) great fatigability and general malaise; (2) dizzy and fainting spells; (3) loss of weight; (4) constipation; (5) pain and tenderness in the right iliac fossa; (6) very severe and constant headaches.

Family History. The patient is the youngest of three living children. One brother died suddenly in infancy, cause unknown. The

2. While reduction in basal metabolism is sometimes found, it is by no means constant, and Dr. Engelbach now considers its presence or absence of little consequence in the diagnosis of posterior lobe hypofunction. (Personal communication.) There is no question that changes in metabolism do occur, as evidenced by the fat deposition, but these changes may produce little or no alteration in oxygen consumption. When there is a marked deviation of the basal metabolism from normal, its cause should be sought for in the thyroid function.

father, brother and one paternal uncle are very tall and slender and of eunuchoid types. The family history is otherwise negative.

Menstrual History. Menstruation began at the age of thirteen. The periods have been regular every 28 days since the onset, and of three or four days' duration. *The onset of the present symptoms caused absolutely no change in them.* She has always had slight dysmenorrhea, but she is sure that *it has not been aggravated by her present trouble.*

Past History. The subject had the usual childhood diseases. She had scarlet fever in early childhood and a severe attack of typhoid fever at the age of twelve years. She has always been tall for her age, and *grew so rapidly that at fourteen she had practically reached her present size.* She thinks that she has grown very little in height since then, but that her hands and feet have enlarged. She had influenza in 1918. In June and July, 1918, she was confined to bed because of pain in the right iliac fossa, which was diagnosed as appendicitis. In November, 1918, appendectomy was performed. The patient states that the appendix was not ruptured and that no drains were used. A few months after the operation she began slowly to develop dragging and pulling pains in the right iliac fossa. Until about one year ago the patient was in perfect health and was fond of skating and other outdoor sports, but has been unable to participate in them since the onset of her present symptoms.

History of the Present Illness. The patient has not been feeling well for about one year, but the symptoms for which she now seeks relief have had a duration of about six or eight months and have been getting progressively worse. In the early fall she weighed 140 pounds, but has been slowly losing weight and now weighs 126 pounds. About six months ago she began to have fainting spells. She usually feels weak and short of breath before these attacks come on, but there is no definite aura. Loss of consciousness is not complete, but she usually falls and is not able to protect herself, but so far has not been injured. There is no coma following the attacks, and after a short rest she is able to continue her work. These spells are more apt to come on when she arises from a sitting or recumbent posture, and have occurred about once every two or three weeks. She fainted twice the week before entering the hospital. There is no tinnitis aurium preceding or during the attacks. Whenever she arises from a sitting or recumbent posture she becomes dizzy and faint, and frequently has to sit down again to recover her balance before walking. These dizzy spells have no definite rotatory nature and she never has them when she is lying down. She always has a tired, languid feeling and is easily fatigued by even slight exercise. She does not feel sleepy or fall asleep during the day, but is mentally inert. She sleeps well at night, usually for eight or nine hours, but feels tired in the morning. Ordinary walking is not accompanied by dyspnea, but walking upstairs causes some breathlessness. Several months ago she noticed that her feet would swell slightly during the day and that her shoes would feel too tight at night, but this has been absent for the last month or more. She has never noticed any definite edema. The headache is present on arising in the morning and continues all day; in fact, she is seldom free from it, at times even waking up at night with it. It is very severe and throbbing in nature, is felt principally deep between the temples, and is made worse on change of posture. The pain in the right iliac fossa developed slowly some months after appendectomy. She describes it as dragging and pulling in type, "like something was attached to the skin." This sensation is especially marked when lying on the left side. It is not influenced by menstruation or defecation, but is worse after walking or running. She has suffered from slight constipation for several years, but it has

been getting progressively worse during the last year, and for about two months before entering the hospital she was unable to have a bowel movement without a cathartic or enema. She never has a vomiting attack. There is no nocturia, polyuria or painful micturation, no cough or night sweats, and no polydipsia. The appetite was fairly good until about two months ago, but for about two weeks before entering the hospital she felt too miserable to eat and took only a little tea, toast and fruit.

PHYSICAL EXAMINATION JULY 23, 1922

The patient is very tall and thin, with muscular development about proportional to the size. There is marked kyphosis in the upper lumbar region. The hands and feet are very large. She appears very miserable, and when she arises from the recumbent to the sitting or standing posture her distress is evident. The facial expression, movements and attitude all indicate a feeling of severe general malaise. She answers questions quickly and intelligently. The complexion is sallow; the mucous membranes are not especially anemic. The skin is warm and moist. She weighs 126 pounds.

Measurements were as follows: (1) from vertex to middle of symphysis pubis, 88 cm.; (2) from middle of symphysis to floor, 88 cm.; (3) height, 176 cm. (5 feet 10.4 inches); (4) span of arms, 175 cm.

Head. The head is large but well formed and in proportion to the body. The hair is fine and thin. The scalp is negative. There is no pain on light percussion of the skull, and no mastoid tenderness. There is slight equal tenderness over both supraorbital notches. The nose is large, with pointed tip and straight bridge. The malar bones are prominent. The lower jaw is prominent, with slight tendency to prognathism. The teeth are in good condition, no crowding, the upper incisors large and lateral occlusion good. The pharynx and tonsils are negative. The tongue is large and protrudes in mid line. The pupils are dilated but equal and regular; they react normally, showing hippus. The movements of eyeball are normal. There is very slight lagging of the upper eyelids. There is no exophthalmus.

Neck. Rather marked pulsation is seen in the suprasternal notch. There is slight systolic bruit over the carotids. There are a few small, hard lymph glands near the greater cornu of hyoid bone and posterior to the sternomastoid. No distended veins are observed. *The isthmus of the thyroid is visible and palpable, and the neck is full in the region of the two lobes.* The gland is soft, however, and contains no palpable masses. There is no abnormal pigmentation around the face or neck.

Thorax. The thorax is long and narrow, but well formed. The costal angle is acute. Litton's sign is present on both sides. The breasts are small, well formed and virginal in type. The hair distribution is normal. The cardiac findings are negative in regard to size, rate, rhythm and sounds. The respiratory movements are equal and regular. Tactile fremitus is normal. The percussion note is of normal resonance throughout. Breath sounds are normal except in the right apex posteriorally, where they are probably more bronchovesicular than normal, and in the left apex posteriorally, where there are a few soft crepitant rales which disappear after coughing and deep breathing. Vocal fremitus is normal except in the left apex posteriorally, where it is slightly increased.

The chest was again examined about one week later by Dr. Albert Taussig, and these signs, in the apices posteriorally, were found to have disappeared.

Abdomen. The abdomen is slightly scaphoid. It moves normally on respiration. There is an old appendectomy scar. There is no

abnormal hair or fat distribution. The pubic hair line is straight. There is a very marked cutaneous vasomotor reaction in the chest and abdomen, which consists of a deep red line appearing every time the skin is gently stroked. This line appears immediately and stays for a long time. The abdominal reflexes are hyperactive but equal on both sides. There is no rigidity or tenderness above the umbilicus. The liver and spleen are not palpable. There is marked cutaneous hyperalgesia between the appendectomy scar and the umbilicus, but not over the scar itself or below it; protective muscle spasm is also present in this region. There is little or no pain on deep pressure in this region, most of the hyperalgesia being cutaneous. The supra pubic region is negative.

Extremities. Upper. Axillary hair is normal. There is no abnormal hair distribution on the arms. The axillary and epitrochlear glands are not palpable. The biceps and triceps reflexes are normal. The hands are very large, with wide wrists, but well proportioned. The fingers are long but neither tapering nor clubbed. The nails are of normal size and not brittle; lunar markings are prominent. There is a coarse, gross tremor of the extended arm and hand, but no fine tremor of the fingers or hand. *Lower.* No abnormal hair distribution is seen. The knee and ankle reflexes are equal and normal. The feet are large and well proportioned. The toes are long, the nails normal.

Vaginal Examination (7-23-22), Dr. R. S. Tilles. The external genitalia are well developed. The hair distribution is normal. The outlet is nulliparous. The vagina is normal. The cervix is slightly softened and points downward and backward. The uterus is forward and somewhat larger than normal. The fundus is long and narrow, lies behind the symphysis pubis, and can be felt here on abdominal examination. Between the cervix and fundus there is a definite area of softening, which finding in the presence of a different history would resemble a sign of pregnancy. The adenexal region is negative. The culdesac is empty. *Diagnosis:* The pelvic condition is negative and does not account for the general symptoms.

January 8, 1923. A second vaginal examination was made on this date (five and one-half months after the first examination). The pelvic conditions were essentially the same, so that the possibility of a pregnancy can be definitely eliminated.

Ear, Nose and Throat Examination. No pathological condition was found to account for the loss of weight and headaches.

Blood Pressure. Determinations were taken in the recumbent position. The systolic pressure was found on several occasions to vary between 100 and 114 mm., and the diastolic between 68 and 80 mm. The pulse pressure was always about the same, being between 30 and 35 mm.

SPECIAL AND LABORATORY EXAMINATION

Urine (single uncatheterized specimen.) The urine is acid. Albumin, sugar and diacetic acid are negative. Acetone is positive. Many W. B. C. were found, R. B. C. rarely, and no casts. The acetone was probably due to starvation acidosis and disappeared after the patient was put on a sufficient diet.

Blood. Cytologic. R. B. C. count is 3,640,000; W. B. C., 11,200; Hb., 70%; polymorph., 74%; small mono., 24%; large mono., 2%; Eosino., 0%; Baso., 0%. The stained smear is normal. *Wassermann.* The test is negative in both alcoholic and cholesterinized antigens. *T. B. Comp. Fixation.* Negative.

Chemical. Non-protein nitrogen is 42 mg. For the carbohydrate tolerance, see Chart 1.

Basal Metabolism. An average of three separate determinations which were well controlled and checked gave *plus 23 per cent.*

Temperature. The temperature on admission to the hospital was 99.4°. For a period of 21 days following this, the morning, evening and occasional noon temperatures were found above normal only five times. These rises occurred at different times of the day, and only once reached 99.5°. For the remaining 16 days the readings were between 97° and 98.6°, and for six days during this time the temperature was constantly subnormal.

Pulse. The pulse rate ranged between 60 and 80 during the 21 days of observation.

X-ray Examination. Chest. The lung fields, including the apices, are clear. The diaphragm moves fairly well. The angles are clear and sharp. Hilus shadows are slightly fused. The heart and vessels are narrow. The heart is of vertical type. *Cecal Region.* No evidence of adhesions are found. *Hands.* The hands have long phalangeal bones, the terminal ones showing slight mushrooming. The carpal and metacarpal bones are somewhat enlarged. *Sella Turcica.* This structure is somewhat small; the clinoid processes appear normal; otherwise negative.

POSTURAL BLOOD PRESSURE CHANGES, JULY 24, 1922

Posture	*Systolic*	*Diastolic*	*Pulse Pressure*	*Pulse Rate*
Lying	110	80	30	73
	114	78	36	72
Sitting	102	84	18	101
	104	80	24	100
Standing	98	78	20	132
	98	80	18	120

The striking drop in systolic pressure, producing cerebral anemia, is one explanation for the fainting and dizzy spells caused by changes of posture. The fact that the diastolic pressure remains practically constant indicates that the peripheral resistance in the arterioles is more or less perfectly maintained. The fall in systolic pressure can be partially accounted for by the combination of visceroptosis and sparsity of extra perioneal and omental fat, which, combined, allow a fall in the intra-abdominal pressure when the upright posture is assumed, with a consequent momentary stagnation of the blood in the portal system and large abdominal veins. This explanation, however, does not account for the persistent low systolic pressure in the recumbent posture or its relation to the endocrine dyscrasia.

GOETSCH TEST, JULY 25, 1922

Time	*Systolic*	*Diastolic*	*Pulse Rate*
Before	100	68	68
	102	70	68
Three min. after injection of 0.5 cc. of 1-1000 Adrenaline Cl.	148	86	93
6 minutes	142	84	76
9 minutes	134	80	72
12 minutes	130	78	72
15 minutes	130	68	78
18 minutes	128	66	72
21 minutes	120	70	72
24 minutes	118	66	72
27 minutes	116	..	80
39 minutes	118	68	80
45 minutes	118	68	80
55 minutes	118	68	72

Subjective signs and symptoms consisted of increase in the headache, marked pulsation in the vessels of the neck, marked pallor, sighing respirations, and slight tremor. Proper precautions were taken to eliminate the psychic element. The test is considered positive.[3]

PITUITRIN TEST, JULY 30, 1922

Time	*Intestinal Cramps*	*Nervous Symptoms*	*Pallor*
Three min. after 1 cc. of Pit. (S) intramuscularly ..	absent	none	no increase
6 minutes	absent	none	pos. slight incr.
8 minutes	very slight	none	no increase
11 minutes	absent	none	no increase
16 minutes	absent	none	slight incr.
23 minutes	absent	none	no increase

This test was originally used by Engelbach and Tierney to determine the presence and degree of posterior lobe insufficiency. They found that a much larger dose was required to give the intestinal reaction (cramps followed by evacuation) in cases with definite posterior lobe insufficiency than in normal individuals. They later decided that while the above was true in some cases, it was not constant enough to allow definite conclusions to be drawn from it.

An interesting feature in this case is the fact that the first test was entirely negative, but after the patient was put on treatment a gradually decreasing tolerance was noted, so that after a short time 1 cc. of Pituitrin (S), intramuscularly, produced intestinal cramps and evacuation, and several months later definite intestinal cramps were obtained with 0.5 cc.

DIFFERENTIAL DIAGNOSIS

Early Pulmonary Tuberculosis. This was one of the first conditions to be considered. The symptoms in general are characteristic. However, the negative x-ray and physical findings in the chest, negative compliment fixation test, absence of cough, laryngeal symptoms, night sweats, and daily temperature elevations, and finally the excellent response to treatment, seem to be sufficient to rule out this condition.

Neurasthenia. As our knowledge of medicine in general and endocrinology in particular increases, those obscure symptoms formerly united under the heading of neurasthenia are gradually being unraveled, and from them tangible entities are being established. The general reactions of this patient, her former excellent health, the absence of etiological factors, and the positive evidence of markedly deranged metabolism which returned to normal as her symptoms abated under treatment, are certainly sufficient to eliminate this diagnosis.

3. The value of the Goetsch test in the diagnosis of hyperthyroidism is very doubtful. It has been reported positive in many cases which showed no other evidence of hyperthyroidism, so that a negative test assumes more importance than a positive one. It has been included here, with a full realization of the questionable value, simply to give complete data.

Ménierè's Disease. The attacks of vertigo are in no way characteristic of this condition and it can be dismissed without further explanation.

ENDOCRINE DYSCRASIAS

Hypogonadism. The patient's size and general development might at first sight make this diagnosis seem reasonable, but a careful analysis of the findings absolutely eliminates it. The most important evidence against this diagnosis is the normal development of the external genitalia, uterus, ovaries, secondary sex characters, and the fact that menstruation began at the usual age and has continued normally until the present time.

Adrenals. There is no absolute evidence that hypofunction of the adrenals exists. The low blood pressure, asthenia, etc., while characteristic of this condition, are equally characteristic of hypofunction of other glands, especially the posterior lobe of the pituitary. While most writers claim that these syndromes are pluriglandular and usually involve the adrenals, the excellent response to pituitary treatment in this case shows that if hyposecretion of the adrenals does exist it is secondary, and is at least partially rectified by restoring the normal pituitary balance.

Pituitary. Since the two lobes of this gland have such widely different functions, it is necessary to analyze them separately.

Anterior Lobe. In this case there is some evidence in favor of *preadult hyperfunction* of the anterior lobe, and quite definite proof that this lobe is *not hypofunctioning* at the present time. The following points are in favor of preadult anterior lobe hyperfunction: (1) the history of very rapid growth before adolescence, so that the present height of 5 feet 10½ inches was reached by the age of 14 years; (2) the hands are the type "en longe"—large but well-proportioned with wide wrist and palm, and long fingers which show some tufting of the distal phalanges; the lunar markings of the nails are well developed; the feet show the same characteristics; (3) large, well-proportioned head; (4) prominent malar bones and mandible, with slight tendency toward prognathism of the latter; (5) well-developed and preserved teeth showing large upper incisors and good spac-

ing; (6) perfect development of the sex organs, with a tendency to over-development of the uterus.

In the introduction to this paper attention was called to the fact that those cases which begin with preadult hyperfunction of the anterior lobe have a remarkable tendency to later pass into the hyposecretory state, involving one or both lobes. In this case there is sufficient evidence to show that the anterior lobe has *not* been involved in the change to hypofunction, for if it had disturbances in menstruation would accompany the change. Repeated questioning on this point shows that the regularity, duration, and amount have remained normal in spite of the marked constitutional symptoms. It is, however, not possible, at the present time, to say whether the anterior lobe is still hyperfunctioning or has returned to a normal state. Observation for a long period of time will settle this point by revealing the presence or absence of beginning acromegaly.

Posterior Lobe. The continuous low and unstable blood pressure, headaches, increased carbohydrate tolerance, obstinate atonic constipation which has become worse as the symptoms progressed, weakness, great fatigability, and increased tolerance to pituitrin are all characteristic of hypofunction of this lobe. This diagnosis is further substantiated by the response to treatment and the decreasing tolerance to pituitrin which accompanied improvement.

Hyperthyroidism. Slight hyperthyroidism has very frequently been found to accompany hypersecretion of the anterior lobe of the pituitary gland (2). The proofs of its existence in this case are *the slight enlargement of the thyroid gland, increased basal metabolism, loss of weight and a positive Goetsch test.* This complicating slight hyperthyroidism has to some extent prevented the full development of the signs due to posterior lobe pituitary hypofunction. Under function of the pars nervoso of the pituitary and hypersecretion of the thyroid have exactly opposite effects on metabolism, fat deposition, carbohydrate tolerance, temperature, pulse, blood pressure and intestinal peristalsis, and when these two conditions are coexisting a balance of function must result. In this case the *increased basal metabolism,* and the *absence of pituitary obesity* are probably due to hypersecretion of the thyroid, which, however, has not been suf-

ficient to overcome the effects of hypopituitarism on the *carbohydrate tolerance, blood pressure, intestinal peristalsis,* and *temperature.*

Diagnosis. The case was diagnosed as follows: (1) preadult hyper-function of the anterior lobe of the pituitary gland, followed by postadult hypo-function of the posterior lobe, the anterior lobe either remaining hyper- or becoming normal in func-

tion; (2) slight hyperthyroidism; (3) cutaneous hyperalgesia of the abdominal wall due to impingement of cutaneous nerves

These pictures were taken several months after treatment had been started, at a time when the patient was well on the road to recovery.

by the scar; possible postoperative adhesions to the parietal peritoneum.

TREATMENT AND PROGRESS

On 7-30-22 the patient was started on the following treatment: 10 grains of pituitary extract (whole gland) by mouth, after each meal and at bedtime, subcutaneous injection of 1 cc. of pituitrin (S) to be given twice per week.

On 8-12-22 she left the hospital apparently feeling better, but the change was so slight and the time so short that no definite conclusions could be drawn. She was instructed to keep on taking the 40 grains of pituitary extract daily and to return to the hospital twice per week for the injections of pituitrin. She was also instructed to get 8 or 9 hours' sleep, to take short daily walks as soon as she was able, to eat regularly and to drink large quantities of milk.

On 9-20-22 the subject weighed 142½ pounds, a gain of 16¼ pounds after 7 weeks of treatment. There has been a gradual amelioration of all symptoms. The headaches have slowly disappeared and she now has been entirely free from them for the last two weeks. She does not have the attacks of vertigo when she arises from a sitting or lying posture, and has not had a fainting spell since she left the hospital. While she was in the hospital it was found necessary to give daily enemas or cathartics to produce bowel movements, but she now states that she has daily spontaneous evacuations without these measures. The appearance is also much improved, the eyes are bright and full of expression, and the dull, worried, haggard look is gone.

POSTURAL BLOOD PRESSURE CHANGES, SEPT. 20, 1922

Position	*Systolic*	*Diastolic*	*Pulse Pressure*	*Pulse Rate*
Lying	128	82	46	72
	126	80	46	76
	128	84	44	..
Sitting	122	84	38	88
	120	86	34	..
Standing	118	88	30	120
	118	90	28	..
	120	92	28	..

When the above figures are compared with those obtained 7-24-22 a great improvement is noted, and it is now clear why the fainting and dizzy spells, formerly encountered on change of posture, are no longer present.

On 9-24-22 a second carbohydrate tolerance test was done and a rather marked decrease in tolerance was noted. See Chart 1 for explanation and comparison of the curves.

9-27-22. *Basal Metabolism.* An average of two separate determinations gave *minus 5.8 per cent.* The determinations were well controlled and done under favorable conditions.

GOETSCH TEST, SEPT. 30, 1922

Time	*Systolic*	*Diastolic*
Before injection	128	80
Three min. after injection of .5 cc. of 1-1000 Adrenaline Cl.	150	88
6 minutes	148	80
9 minutes	146	78
12 minutes	142	80
15 minutes	132	78
18 minutes	132	80
21 minutes	140	78
24 minutes	140	80
27 minutes	132	78
30 minutes	136	80
1 hour and 10 minutes	128	80

Subjective signs and symptoms, such as increased respiration, nervousness, throbbing pulsations in the vessels of the neck, etc., were present but much less marked than on the former occasion. According to the standards set by Goetsch, the test would still have to be considered positive, but when compared with the test done 7-25-22 some marked differences are seen. To begin with, the systolic pressure is now 28 mm. higher than it was formerly. The height reached by the systolic pressure after injection is practically the same—148 mm. formerly and 150 mm. now—but owing to the difference in the systolic pressure before injection, the total rise in pressure is now much less —48 mm. formerly and 22 mm. now. Just how this change is to be interpreted I am unable to say.

PITUITRIN TEST, SEPT. 30, 1922

Time	*Reaction*
3 min. after 1 cc. of Pituitrin (S) intramuscularly	Headache, slight abdominal cramps and slight pallor.
25 minutes after.....	The abdominal cramps have been increasing in severity and the patient has just had a bowel movement. Pallor is very marked. Is having severe psychic reactions in the form of crying, etc.
35 minutes after.....	Abdominal cramps still present, but much less severe. Pallor less. Psychic reaction is over.
40 minutes after.....	Reaction over.

The above reaction is positive. Two months ago, when the same test was done, before treatment was started, an entirely negative reaction was obtained, i. e., little or no intestinal cramps and no vascular or psychic reaction. There is therefore a decrease in the tolerance to pituitrin.

On 3-4-23, all treatment was stopped. For about three weeks her condition remained unchanged, but after this she began to develop the same symptom complex that had first brought her to the hospital. None of these symptoms, however, reached the grade of intensity that had prevailed at that time. On 4-24-23, she was again started on whole gland extract, 40 grains by mouth daily, and this was continued until 5-18-23 with a slight amelioration of all symptoms. On this date she was started on 1 cc. of Pituitrin (S) subcutaneously twice per week in addition to the whole gland by mouth. The improvement was now more marked and continued until she was again entirely free of all previous complaints. At the present time, after one and one-half years of observation, there has been no return of symptoms, but the above treatment has been intermittently continued for the greater part of this time.

DISCUSSION

There is always a certain amount of psychic, subjective improvement apt to occur in these cases shortly after treatment is started; but if this is the only basis for improvement it will usually disappear after a short time and the former symptoms return. In this case sufficient objective and metabolic changes were brought about to eliminate the purely psychic element of amelioration. These changes consist of gain in weight, establishment of a normal and stable blood pressure, reduction in basal metabolism, restoration of sugar tolerance to almost normal, decrease in the tolerance to pituitrin, and the disappearance of an obstinate, atonic constipation.

Increased basal metabolism and loss of weight are contrary to what we should expect to find in hypofunction of the posterior lobe of the pituitary, and are attributed to a complicating slight hyperthyroidism. If this explanation is correct, it seems unreasonable to believe that the basal metabolism would be restored to normal and a gain of weight brought about by pituitary treatment. This amelioration of hyperthyroid symptoms by treatment with pituitary extracts, however, has been noted clinically by other investigators; Richter (3), Pal (4), McGraw (5), and Hofstatter (6) have all reported cases which support this view. Engelbach has observed, in addition to the disappearance of hyperthyroid symptoms, a reduction of basal metabolism as demonstrated in this case.[4] These observations, however, have not been well enough controlled, or sufficiently checked by others to allow definite conclusions to be drawn from them, but, if correct, offer an explanation for the equivocal changes found in this case.

The effect of the anterior lobe of the hypophysis on basal metabolism is unsettled, and I have followed Engelbach in believing that its effect is nil. Aub and Taylor (7), in a recent review of the data on this subject, state: "Work on the pituitary suggests that hypersecretion of the anterior lobe may cause a slight rise in metabolism, although this fact is not yet well established."

Engelbach, Cushing, and the majority of clinicians, believe that the development of pituitary obesity depends on hyposecre-

4. Personal communication.

tion of the posterior lobe, and I have attributed its absence in this case to two factors; first, the patient was seen and treated early, possibly before the disorder was fully established, so that the obesity may have developed later; second, the effect of the hyperthyroidism may have been sufficient to totally prevent its development. Engelbach (8) finds evidence to believe that if hypofunction has been preceded by hyperfunction of the posterior lobe, then the typical obesity does not develop. There was no evidence, however, of preceding hyperfunction in this case. There is another possible explanation based on experimental data, namely, that hyposecretion of the anterior lobe is the factor which causes the development of pituitary obesity.

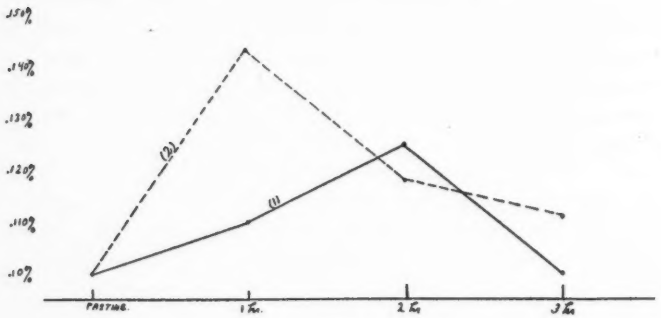

CHART I
CURVE 1 7/29/22
CURVE 2 9/24/22

Pure dextrose, 1.75 grams per kilo, was given in both instances. The first curve is definitely lower than normal. The second curve is a normal type, and the maximum height is only slightly below the minimum height of a normal curve. We consider a normal curve to be one that reaches its maximum height (between 0.15% and 0.18%) in one hour, and returns to normal at the end of three hours. Simultaneous specimens of urine were dextrose free in both tests.

Beck, in Endocrinology and Metabolism (9) states, "Experimentalists generally believe that the adiposity of dystrophia adiposogenitalis is due to hypofunction of the anterior lobe, because removal of the anterior lobe, or posterior lobe plus a large part of the anterior lobe, will give adiposity, while simple removal of the posterior lobe will not." If this is true, then we are mistaken in considering the Lorrain-Levi type of hypopituitarism as due purely to anterior lobe hypofunction, because in this type the typical pituitary obesity is not present (10). The

excellent response of many of these cases to treatment with anterior lobe extracts makes the experimental evidence seem doubtful, and further work in both clinic and laboratory will be necessary to clear up this question.

The relation of hypopituitarism to fainting attacks has been emphasized by Pierce (11). He reports cases in rapidly growing adolescents with fainting attacks, fatigability, low blood pressure, etc., due to hypopituitarism, who are benefited by by treatment with pituitary extract. He makes no attempt to analyze the symptoms from the standpoint of lobar function, but apparently attributes them to hypofunction of the whole gland.

The possibility of spontaneous cure or improvement in these cases, by enlargement and increased function of the pituitary, has been observed by Timme (12). He reports a series characterized by headaches, fatigability, low blood pressure, low blood sugar and vasomotor instability, many of which improved without treatment, and in these cases he was able to demonstrate that erosion and enlargement of the sella turcica had occurred. All of his cases were improved by continuous feeding of pituitary extract. He believes that the syndrome is pluriglandular, involving the thymus, adrenals and pituitary, with hypofunction of the latter as the primary factor.

Cases similar to the one under discussion are by no means uncommon,[5] and it is of great importance to differentiate them from *primary* slight hyperthyroidism in order to avoid needless surgical or other therapeutic measures. If the signs of a pluriglandular syndrome with primary pituitary disturbance are recognized, it may be possible totally or partially to relieve the hyperthyroid and other symptoms by restoring normal pituitary balance.

In conclusion I wish to thank Dr. Albert Taussig, Chief of the Medical Service of the Jewish Hospital, for his interest and permission to publish the case, and Dr. Wm. Engelbach and Dr. C. H. Neilson for their kindness in reading the manuscript and offering many valuable suggestions and additions.

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5. Personal communication from Dr. Engelbach.

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END RESULT IN THYROTOXICOSIS

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The following case is reported in order to increase the number of case histories in the literature depicting the conditions found at autopsy in cases of thyrotoxicosis treated by operative methods. Up to the present, we have obtained only the reports

FIGURE 1

as to the immediate operative effects and very few reports showing the ultimate effects and the conditions under which the patient died.

The patient in the following protocol had been operated on twice and had also been treated with the injection of boiling water, and yet died some years later with all the symptoms of acute thyrotoxicosis and evidence of proliferation of the thyroid gland.

George Martin, a white male, aged 50 years, was first admitted to the General Hospital on April 15, 1921. He was a widower; occupation, cook.

The *family history* was negative.

FIGURE 2

Personal History: Chief Complaints. The patient complained of (1) swelling of the feet and ankles; (2) weakness; (3) palpitation of the heart; (4) enlargement of the thyroid gland.

The present trouble is apparently an exacerbation of a condition existing from the age of twelve. Enlargement of the gland and bulging eyes were the first symptoms noticed. Other symptoms appeared,

and twelve years ago part of the thyroid gland was removed while the subject was in California. This was followed by a cessation of symptoms, and the patient was able to work until three weeks ago, when the old symptoms reappeared, together with loss of weight (30 pounds in two months), and also an enlargement of the thyroid gland.

Physical Examination. Positive Findings. (1) the face and neck are very red and flushed. (2) The eyes are bulging, especially marked in the left. All signs of exophthalmos are present. (3) The thyroid is enlarged, with depression in the region of the isthmus. The en-

FIGURE 3

largement is bilateral, but is more marked on the left. The gland is firmer on the left. A scar shows the site of the previous goiter operation. (4) The heart sounds are irregular in force and frequency. The second sound is accentuated and sharp. A low-pitched systolic murmur is heard at the apex and base; it is best heard over the aortic area. The heart is enlarged downward and to the left. The heart rate is 80 to 100. (5) There is moderate sclerosis of the radials. Marked pulsations in the neck are observed. The blood pressure is

60 to 160. (6) There is a fine tremor of the tongue and fingers. (7) Co-ordination and mentality are good. (8) Brownish discoloration and healing ulcers are noted on both legs from the middle to the lower third.

Provisional Diagnosis was as follows: (1) exophthalmic goiter; (2) myocarditis; (3) dilated aorta; (4) lues, tertiary.

Laboratory Reports. (1) Urinalysis on three occasions was negative. (2) The blood count is: Hb., 75 per cent; erythrocytes, 4,200,000; leucocytes, 4,000; differential, p. m. n., 52; small lymphocytes, 40; large lymphocytes, 5; large mononuclears, 9; and transitional, 1. (3) The Wassermann determination is 4 plus. (4) X-ray examination, 4-18-21, showed a very large heart with much density about the mediastinum and chronic fibrosis throughout the chest. On 7-6-21 there was density in the upper midline suggestive of an enlarged thymus.

FIGURE 4

The patient was treated medically by rest in bed, digitalis and antiluetic therapy until the symptoms were alleviated sufficiently for operation, which was done on June 3, 1921.

Operative Report. As anesthetics novocain and ether were used. A portion of the left lobe was removed—two by three inches. Bleeding was profuse. The superior thyroid artery was ligated. Microscopic examination of the tissue removed showed extreme hyperplasia throughout. Possibility of malignancy was noted.

On June 24, 1921, under local anesthetic, 2 cc. of boiling water was injected into the right lobe.

The patient was discharged on July 13, 1921, in a much improved condition.

SECOND ADMISSION—JAN. 9, 1924

Chief Complaints. The subject complained of: (1) a choking sensation; (2) nervousness; (3) a very definite psychosis and status not dependable. He was not oriented as to time or place.

Physical Examination: Positive Findings. (1) The face is flushed. (2) The eyes are bulging, the conjunctiva congested. The right pupil is larger than the left; both react to light and accommodation. (3) There is an old scar on the neck. The thyroid is enlarged bilaterally. (4) The heart is enlarged down and to the left. The sounds are fast and irregular. No murmur can be heard. (5) Healed ulcers are seen on the anterior surface of both legs.

Laboratory Reports. (1) Urinalysis is negative. (2) Blood counts and smears are normal except for 9 mgs. calcium per 100 cc. blood.

The patient had to be put in the psychopathic ward. He did not respond to medical treatment on account of his constant psychosis and lack of co-operation. He developed pneumonia after two weeks. While febrile his delirium lessened, but during convalescence his motor mania returned. He was sent back to the psychopathic ward. Two days later he developed facial erysipelas and died Feb. 13, 1924.

Autopsy Report. The lungs showed broncho-pneumonia in the lower left lobe—of the terminal infection type. The *heart* showed several sclerotic changes. The *aorta* showed occasional atheromatous changes. The *liver* was congested. The *kidneys* showed an interstitial nephritis of low degree. The *thyroid* showed hyperplasia with a tendency to infiltration in the spaces about all the surrounding structures. The consistency of this hyperplastic tissue was of a curious uniformly livid type, reminding one of malignant degeneration.

The microscopic slides show proliferation of the glandular elements of the thyroid with a decrease in the colloid. There is considerable round cell infiltration and other evidence of rapid growth. Dr. Hertzler, who saw these slides, classifies the picture as that of thyro-

toxicosis rather than that of exophthalmic goiter. Dr. Trimble, however, favored a diagnosis of beginning malignancy. The accompanying photomicrographs illustrate some of the difficulty of interpreting the nature of the process.

The case shows how little operative treatment gets at the cause of the proliferation of thyroid tissue. The history shows also the effects of an overactive thyroid rather than those of a carcinoma.

RICKETS AND PARATHYROIDS

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It is now ten years since Erdheim (1) pointed out the probability of a relation between rickets and parathyroid function. He developed the thesis from the observation that a marked enlargement of the parathyroids frequently occurs during spontaneous rickets. He interpreted this enlargement as the consequence, not the cause, of the rachitis. The correctness of this interpretation will be discussed during the analysis to be given in this paper.

Both rickets (2) and parathyroid deficiency (3) produce retardation of ossification of the bones of young and growing animals. Because of the presence of this common symptom in the two disturbances, there has been a tendency to consider parathyroid deficiency as an etiological factor in the distortion of bone growth in rickets, in the sense that the dietary defect acts to retard ossification through intermediation of the parathyroids. Such a contention is untenable in the light of recent investigations.

Now retardation of ossification occurs when the organism lacks the ability to lay down the essential calcium salts in the bones, or when the essential components of these salts are not available in requisite amounts.

While it is possible that the former type of deficiency participates in rickets and after parathyroidectomy, we have no certain evidence that such is the case. On the other hand, there is evidence available which demonstrates not only a lack of the elements essential for the formation of osseous tissue, but also a disturbance of the phosphorus-calcium ratio which McCollum (4) has shown to be so important in bone formation. It is this deficiency and the disturbance of the ratio which allows a differentiation of the two pathological conditions.

The lack of available bone building materials and the disturbance of the phosphorus-calcium ratio is different in rickets

than in parathyroid deficiency. It is this fact which allows the elimination of the parathyroid factor as a participant in the retardation of ossification in rickets.

Let us first consider rickets. In this disorder there is less phosphorus in the blood than is found in normal persons. On the other hand the calcium content of the blood is essentially within normal limits (5). In other words, the phosphorus-calcium ratio is decreased. Since the formation of bone of normal composition depends upon an adequate supply of both phosphorus and calcium in normal ratio, it is obvious that the decrease in the one element (phosphorus) with the other (calcium) remaining normal—as occurs in rickets—is the immediate important factor in the retardation of ossification in this disease. This belief is substantiated by the fact that the feeding of cod-liver oil to rachitic animals raises the phosphorus content of the blood and with this increase there occurs a release from inhibition of ossification (6).

It is evident, then, that the action of the lack of essential vitamin on ossification is exerted in large part through its effect on the phosphorus side of the phosphorus-calcium ratio.

Turning now to the consideration of the condition of parathyroid deficiency it is seen that a picture of an entirely different type is presented. Here calcium instead of phosphorus is low in the blood, calcium is lost from the body (7) and the phosphorus of the blood tends to be increased (8) and less is excreted in the urine. This is reflected in the composition of the ash of the bones in which a decrease in calcium per cent and an increase in phosphorus per cent obtains (9).

It is evident, then, that the action of parathyroid deficiency on ossification is exerted in large part through its effect on the calcium side of the phosphorus-calcium ratio. An effect which is quite the opposite of that exerted by the vitamin deficiency which produces rickets.

The two mechanisms by which retardation of ossification is produced are thus seen to be distinctly different, although they do produce like end results. This similarity of end result, retardation of ossification, proceeding from opposite types of distortion of the phosphorus-calcium ratio, is understandable when it is realized that an adequate amount of both calcium and

phosphorus in proper ratio is necessary for normal bone substance formation.

Although the foregoing analysis demonstrates that the parathyroids cannot be considered as etiological factors in the production of rickets, there remains the necessity for an explanation of the enlargement of these glands in that disease. Such an explanation is derivable from available data.

A recent study of Grant and Gates (10) showed that radiation of rabbits with ultra-violet light produces an increase in the blood calcium which is accompanied by an increase in the size of the parathyroids. This response parallels Erdheim's (1) observation of parathyroid enlargement in rickets. Correlating these findings with those already given it is evident that a lowering of the phosphorus-calcium ratio causes a disturbance in parathyroid function, probably in the direction of an increased activity. On the other hand, when a parathyroid deficiency exists the opposite reaction is elicited, e. g., an increase in the phosphorus-calcium ratio. Such being the case it is clear that Greenwald's (11) belief that any theory of the causation of tetania parathyreopriva must take into consideration these changes in calcium and phosphorus is well founded. However, it is necessary, I believe, to extend the conception away from circumscribed attention to calcium deficiency as such, such as has occupied workers in this field in the past, and to focus it upon the change in the phosphorus-calcium ratio. On this basis, then, a function of the parathyroids is associated with the maintenance of the phosphorus-calcium ratio, whether directly or indirectly it is impossible to determine at the present time, and a disturbance of this ratio such as occurs in rickets or after radiation with ultra-violet light produces an attempt on the part of these glands to maintain the equilibrium, which attempt is expressed in hypertrophy.

SUMMARY

Although the parathyroid glands are probably intimately concerned in the maintenance of the phosphorus-calcium ratio and hence in ossification as shown by their enlargement when this is disturbed and the disturbance of the ratio in conditions of parathyroid deficiency, yet they are not to be considered as

active participants in the retardation of ossification observed in rickets because of the fact that in rickets the disturbance of the phosphorus-calcium ratio is in the direction of a decrease of this value, while in parathyroid deficiency the distortion is the opposite in direction, that is, an increase in the value of the ratio. Such being the case the two conditions are not to be confused even though the end results—retardation of ossification—are similar.

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Book Reviews

THE AUSTRALIAN JOURNAL OF EXPERIMENTAL BIOLOGY AND MEDICAL SCIENCE.

On March 15, 1924, there appeared the first number of a new quarterly journal, The Australian Journal of Experimental Biology and Medical Science. This journal is published at the University of Adelaide for the Medical Sciences Club of South Australia and it is sustained by the Miss A. F. Keith Sheridan Bequest to the University of Adelaide for medical research. The managing editors are Professor J. B. Cleland and Professor T. Brailsford Robertson. These gentlemen will be assisted in the selection of papers by a board of editors consisting of seventeen well-known and prominent members of medical, biological and veterinary circles in different States of the Commonwealth. It is intended to publish articles embodying the results of original research in bacteriology, biological chemistry, experimental medicine or surgery, experimental pathology, experimental zoology, genetics, immunology, parasitology, pharmacology and the physiology of plants and animals. The first number consists of 37 pages and contains four articles. A. B. Anderson reports his observations on the effect of phloridzin on the mortality from "insulin" hypoglycemia in mice. M. T. Mitchell contributes an article entitled "The Substitution of Taurine for Cystine in the Diet of Mice." O. W. Tiegs discusses the mechanism of muscular action and T. Brailsford Robertson writes upon the influence of hydrolysis upon the capacity of proteins to bind acids and bases.—Med. J. Australia, 1924, i, 317.

THE ENDOCRINE ORGANS. AN INTRODUCTION TO THE STUDY OF INTERNAL SECRETION. Part I, The thyroid, the parathyroids, and the suprarenal capsules. Sir E. Sharpey-Schafer. Longmans, Green and Co., N. Y., 1924, 2 ed., pp. 175.

The first edition of Sharpey-Schafer's monograph well deserved the popularity which resulted in its soon being out of print. A new edition is correspondingly welcome. It is hoped that the second part will soon be available. The work in general follows the lines of the first edition. The literature has been brought up to date in a thoroughgoing way. A surprising num-

ber of the citations refer to articles published since the war. The bibliography is delightfully free from over-stressing the work of nearby investigators at the expense of that of the geographically remote.

One of the most commendable features in a work of this scope is the placing of the references as footnotes to the discussions. It is presumed that the student who desires an exhaustive treatment of any topic will consult the larger works and utilize their more extensively classified bibliographies.

The illustrations are judiciously selected and the typography is excellent. Altogether the work is to be heartily recommended to those desiring a sane, well-balanced treatise of moderate length.—R. G. H.

FUNZIONI E DISFUNZIONI TIROIDES. L. Castaldi, G. Pighini, U. Cerletti, O. Rossi & E. Lugaro. Instituto Sieroterapico Milanese. 8vo, pp. 288, with illustrations.

This is another series of ten lessons of five studies, a continuation of the preceding volume on "Endocrinologia," instituted by the Instituto Sieroterapico Milanese. This year the theme was limited to the thyroid and related topics. Castaldi emphasizes above all the importance of this gland in body growth; Pighini and Cerletti have investigated two endemic diseases, goiter and cretinism, which, as is well known, are directly related to the thyroid; Rossi illustrates other effects of thyroid dysfunction; and Lugaro points out the relations of this gland to psychical functions.—P. M. N.

LA ACCION FISIOLOGICA DE LOS EXTRACTOS HIPOFISIARIOS. Dr. Bernardo A. Houssay, Talleres Gráficos de A. Flaiban, Buenos Aires, 1922. Pp. 277-340.

This is a continuation of Houssay's exhaustive monograph bearing the same title, issued in 1918. In it the literature is brought up to date and nine pages of bibliography added. The author is to be commended for quoting the references in the original rather than in Spanish translation as in the first installment of the monograph.—R. G. H.

Abstract Department

The effect of adrenal substance on the conduct of young white rats. Berman (L.), Endocrinol. e patol. cosituz. (Roma), 1923, **2**, 38-40; abst., Ber. ü. d. ges. Physiol. (Berl.), 1924, **23**, 114.

Twenty-six day old rats were fed for several days with fresh adrenal substance. Increased liveliness, hyperactivity of the musculature, a quarrelsome disposition and hyperirritability were observed. The young females also showed an aggressive attitude toward animals of the same sex. The investigators concluded that the ingestion of suprarenal cortex influenced the combative instincts and caused a condition approaching suprarenal virilism in females.

—M. D. G.

A quantitative estimate of the catalytic power of adrenaline and thyroxin as calorigenic agents and the relative rate of their destruction. Boothby (W. M.) & Sandiford (I.), J. Biol. Chem. (Balt.), 1924, **59**, xl.

The administration of both adrenalin and thyroxin produces in the human being an excess of heat over and above that which would have been produced had the substance not been given. It is possible to construct plots integrating this increased heat production for given weights of thyroxin and adrenalin. This has been done and the significance discussed.—F. S. H.

Results of adrenal extirpation (Uber die Ausfallserscheinungen nach Nebennierenextirpation. I. Mitt.). Bornstein (A.) & Holm (K.), Ztschr. f. d. ges. exper. Med. (Berl.), 1923, **37**, 1-16; abst., Ber. ü. d. ges. Physiol. (Berl.), 1924, **23**, 259.

After simultaneous removal of both adrenals in the dog, death followed in 7 to 12 hours. This time was not prolonged by keeping the body temperature constant, bringing the blood sugar up to normal by using pilocarpine or morphine or by extirpating the pancreas at the same time as the suprarenals so that the dog had a high diabetic blood sugar. Constant infusion of adrenalin did not postpone the time of death. Neither did death depend upon temperature fall, drop in blood sugar or deficiency of adrenalin in the blood. The condition was not altered if any of the three mentioned consequences of adrenalectomy were increased. The chief symptom following adrenal removal is increase in respiration. The amount of respired air rises usually twice, often four fold, both the number of respirations and their depth increasing. The alveolar CO_2 tension

decreases greatly, the O_2 consumption is markedly diminished. The increased CO_2 output of the alveoli is quite noticeable in the blood —the CO_2 combining power of which drops from 50-56% to 30-43%. The over-ventilation after adrenal removal is similar in every respect to that of controlled forced respiration in men. In both cases the acidity of the urine sinks together with the ammonia fraction of the total N; true acapnia results in each case. In both forms of over-ventilation death results through paralysis of the respiratory center—the heart continuing to beat. The symptoms of over-ventilation in acute adrenal deficiency seem, therefore, to have a special significance since a large list of other symptoms of over-ventilation can be identified, such as fall in body temperature, lowered blood pressure, rigidity and twitching of the musculature. The source of the stimulus to the respiratory center which leads to over-ventilation is yet to be disclosed. This condition is not prevented by large doses of morphine.—M. D. G.

Treatment of apparent death of the new-born with intra-cardiac injections of adrenalin (Traitement de la mort apparente du nouveau-né par injection intracardiaque d'adrénaline). Brindeau (A.), Bull. soc. d'obst. et de gynéc. (Par.), 1923, **12**, 467.

Aspiration, and oxygen insufflation having proved inefficacious in bringing to life a new-born infant without cardiac movement, 0.5 cc. of adrenaline was injected into the heart muscle and insufflation was continued. The heart was caused to beat, but the patient died because respiration could not be induced. Meningeal hemorrhage was found at autopsy. Two other subjects reacted similarly.

—F. S. H.

A comparison of the effects of the injection of gum acacia and of the transfusion of blood on the oxidative power of the brain as indicated by alterations in temperature after the injection of adrenalin. Crile (G. W.), Rowland (Amy F.) & Wallace (S. W.), J. Lab. & Clin. M. (St. Louis), 1924, **9**, 309-312.

In the bio-physics laboratory of the Cleveland Clinic it has been shown that adrenalin exercises a specific effect on the oxidative powers of the brain, which is manifested by an increased temperature of the brain in direct relation to the amount of adrenalin injected. Employing this as a criterion, it was found that the oxidative power of the brain is markedly diminished by gum acacia solution, while it is increased by transfusion of whole blood.—I. B.

Heat production in the adrenalectomized frog (Le produzione di calore nella rana privata di capsule surrenali). Gayda (T.), Gior. d. r. Accad. di med. (Torino), 1921, **4s. 27**, 403-404.

After the immediate effects of operative trauma have worn off the heat production always diminishes more if the animals have been

completely adrenalectomized. If the adrenals are not completely destroyed the heat production is good until a few days before death.
—P. M. N.

The human suprarenal cortex in abdominal wounds and in the interesting periods of sex life (Le cortex surrenal humain dans les plaies de l'abdomen et aux periodes interessantes de la vie sexuelle). N. Goormaghtigh, Thesis, University of Grand, 1922.

A detailed description of the cytology and histochemistry of the human suprarenal cortex is given from a normal standpoint. This is followed by a record of observations made on cortical material secured from war victims immediately following death, using cases in which death was due to peritoneal hemorrhage or peritonitis following abdominal wounds. Then follow observations on cortical material obtained at the important periods of sex life secured after death due to accident.

The adult normal cortex of the adrenal is composed of four zones in order from inside to outside as follows:

(a) Juxtamedullary, a thin band composing about one-eighth of the total cortex; it is itself composed of irregular, anastomotic, monocellular cords surrounding the blood capillaries and lymphatics. In man these cells are in immediate contact with the medullary cells. Their secretory activity is manifested by their formation of pigment.

(b) A zone corresponding to the superficial part of the reticularis, composed of parallel columns which are made up of turgescent polyhedral cells with pale and finely granular cytoplasm. The nuclei are spherical and usually contain two nucleoli, but the important morphological characteristic of these cells is that they contain no lipoid in the state of droplets, thus marking the point of the departure of lipogenesis. In the superficial part of this zone is a new cell type, the siderophile cell of Ciaccio: elongated cells located on the surface of the columns and running parallel with them. They are rich in mitochrondria and are usually attached to each other forming cell trains extending into the adjacent zona spongiosum. Their secretory activity is manifested by the appearance of small granules that increase in number while the mitochrondria diminish as the cells extend into the adjacent zona spongiosum. These cells play an important rôle in lipogenesis, the lipoids being nonlabile.

(c) Zona spongiosum, forming two-thirds of the cortex composed of cells resulting from the progressive transformation of the siderophile. The insensible disappearance of the siderophile is brought about by accumulation of a considerable number of large droplets and the diminishing of mitochrondria. These spongiocytes act as lipoid reservoirs and represent the final morphological expression of the lipogenesis. The lipoids are labile.

(d) Zona glomerulosa, a thin layer of cell cords composed

principally of two cell types; a clear pale cell and a dark cell. A few spongiocytes with small droplets may be seen.

The histochemical reactions of the cortical lipoids as regards fat stains and solvents is discussed and systematized.

In peritoneal hemorrhage there is a rapid increase of the labile lipoids in the deeper zones of the cortex (fasciculata and reticularis).

The influence of peritonitis on the cortical lipoids shows that the functional activity is secretory and excretory. Extending over a period of six days there are three excretory and two secretory phases. First there is a discharge of lipoids, then a renewal followed by a second discharge. This in turn is followed by a second renewal and another discharge. During the renewal of lipoids the siderophiles greatly increase in number. The cortex is a regulator of the cholesterine chemistry of the body. The observations show that the outer seven-eighths of the cortex produces an antitoxin (ethers of cholesterine) to aid the organism to combat infection. The inner one-eighth takes no part in this production.

During the important periods of sex life, birth, confinement, menopause, and old age, the juxtamedullary zone shows marked changes in size and activity independent of the other zones, a fact which would indicate that this zone controls manifestations of sex life, especially the secondary sexual characteristics.—E. B. Hanan.

The adrenalin injection test in Basedow's disease (L'épreuve de l'injection d'adrénaline dans la maladie de Basedow). Labbé (M.) & Lambru, Ann. de méd. (Par.), 1923, **14**, 423-430.

The application of the Goetsch test to 10 healthy subjects produced a slight increase in pulse and respiration rate, no glycosuria, and but little hyperglycemia. Palpitation, tremor, asthenia, sweating or rise in temperature were not observed. Ten patients with Basedow's disease responded to the same test as follows: 70% marked hyperglycemia; 80% greater than normal reaction of pulse; oculo-cardiac reflex inverted in all cases. The test is therefore considered as of moderate value only in the diagnosis of Basedow's disease, since all other manifestations were as in the controls. In sympathicotonia, however, the reactions are striking. An analysis of the reactions of the two disorders to the test is given.—F. S. H.

Adrenalin administered per rectum in children (L'adrénaline administrée par voie rectale chez l'enfant). Lesné (E.) & Baruk (H.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 389-392.

Five minutes after the administration of 100 drops of 1-1000 solution of adrenalin by rectum there is a rise of arterial tension both maximum and minimum. The pulse is accelerated and hard. The effects appear in 10 to 12 minutes and progressively diminish.

There is no glycosuria. The same dose administered by mouth has practically no effect.—T. C. B.

The relation of Addison's disease to amyloidosis. McCutcheon (M.), Am. J. M. Sc. (Phila.), 1923, **166**, 197-200.

A report of a clinically typical case of Addison's disease associated with widespread amyloidosis, which involved the cortex of both adrenals. The amyloidosis was believed to have resulted from a large hypernephroma. Amyloid disease does not often cause Addison's syndrome. In this case it was believed that the destruction of the adrenal cortex by the amyloid degeneration was sufficiently severe to determine the appearance of Addison's disease.—J. P. S.

Adrenal hemorrhage in infancy. Rabinowitz (M. A.), Am. J. M. Sc. (Phila.), 1923, **166**, 513-518.

Report of 2 cases of rapidly fatal hemorrhage into the adrenals in two children 18 and 17 months of age, respectively. The condition was characterized clinically by sudden onset in a previously healthy child, rapidly followed by purpura and collapse. The temperature reached 106 degrees in one case and 107.5 degrees in the other. The chief finding at necropsy was a diffuse infiltration of the adrenals, both cortex and medulla, with bright red blood clot. —J. P. S.

Toxicity of cocain as influenced by rate of absorption and presence of adrenalin. Ross (E. L.), J. Lab & Clin. M. (St. Louis), 1923, **8**, 656-660.

In a series of experiments on cats it is shown that adrenalin markedly increases the toxicity of cocain.—I. B.

The influence of disturbance on the glycosuric action of subcutaneous adrenalin injections (Beiträge zur Physiologie der Drüsen. 59. L. Asher. Ueber den Einfluss der Umstimmung auf die glykosurische Wirkung subkutaner Adrenalininjecktion). Tsukamoto (R.), Biochem. Ztschr. (Berl.), 1924, **145**, 176-192.

Normal rabbits excrete from 3 to 3.6 gms. of sugar after one injection of adrenalin. The percentage of sugar in the urine varies with the amount of urine. Too young rabbits cannot be used for such experiments. When the animals are fed **thyroid** preparations and react strongly thereto, an actually lesser glycosuria may be produced, but it comes on much quicker. Other animals respond with an abnormally high glycosuria. The phenomena are explicable on the basis of the double action of the thyroid hormone, e. g., the activation against adrenalin and the lessening of the glycogen store. Removal of blood and replacement by transfusion of Ringer's solution with gelatine produces a delayed reaction to adrenalin.—F.S.H

Malformation of the adrenal glands with the clinical picture of Addison's disease. Wahl (H. R.), Med. Clin. N. Am. (Phila.), 1924, **7**, 1357-1364.

The case reported is that of a married woman of 46 whose illness began 19 years ago with what she called an early menopause. Five months before death there were marked weakness, considerable diarrhea and rapid loss of weight. The skin had become "copper spotted," especially in the palms of the hands. Five weeks before death the systolic blood pressure was 60 and the diastolic was 40 to 42. A clinical diagnosis of Addison's disease was made. At autopsy no evidence of tuberculosis was found, and the suprarenals, though unusually small, were otherwise apparently normal. Microscopic examination revealed an almost complete atrophy of the adrenal cortex, the medulla having enlarged and accumulated many embryonic neurocytes which seemed to have lost the power of differentiation to a functionating tissue. The author suggests that since there is a close relationship between the suprarenal cortex and the genital organs, it is quite likely that with the cessation of menstruation there was a corresponding atrophy of the cortex, which, by the time the patient died, had almost entirely disappeared.—I. B.

Innervation of the thymus, thyroid and parathyroids (Die Nerven des Thymus). Braeucker (W.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1923, **69**, 309-327.

Technical description of the nerve supply to the thymus, thyroid and parathyroid glands based on dissection of human fetuses. The author concludes that the nerves to the parathyorids and thyroid arise from both the vagus and cervical sympathetics and possibly slightly from the glossopharyngeus in case of the thyroid. The nerves to the thymus arise from the upper thoracic and cervical sympathetics and the vagus and on their way to the gland become associated with the cardiac nerves, blood vessels to the thymus and occasionally the phrenic nerve. The nerves to all these glands are closely interwoven with the nerves to the heart and great blood vessels.—A. T. R.

Interrelation of the parathyroids, suprarenals and pancreas. Clark (G. A.), J. Physiol. (Lond.), 1924, **58**, 294-301.

The injection of guanidin into rabbits "produces two effects, the first and more powerful being a stimulation of the sympathetic system causing a hyperglycemia, which is probably augmented by an increased production of adrenalin, and the second a hypoglycemia which can be explained by an increased liberation of insulin due to vagal stimulation."—T. C. B.

Differentiation of human phosphatases (Differenzierung menschlicher Phosphatasen). Forrai (E.), Biochem. Ztschr. (Berl.), 1924, **145**, 54-56.

The ability of **testes, adrenals, thyroid, pancreas** and **spleen** to split various types of phosphoric acid esters was studied. Other organs were included.—F. S. H.

The occurrence of a hypoglycemia-producing substance in bacteria. Little (J. T.), Levine (V. E.) & Best (C. H.), J. Biol. Chem. (Balt.), 1924, **59**, xxxvii-xxxviii.

Bacteria grown in culture media free from substances that may contain insulin, such as peptone, meat, blood, etc., produce a substance which can be extracted by suitable measures and produces hypoglycemia in the rabbit.—F. S. H.

A case of infantilism (Sopra un caso di infantilismo). Pescatori (G.), Gior. di clin. med. (Parma), 1923, **4**, 453-461.

A typical case of infantilism of Brissaud's type is described. The mental underdevelopment was scarcely noticeable in comparison with the marked lack of bodily growth. The author believes this condition to be of pluriglandular origin, caused by hypofunction of the **thyroid** (predominating), **hypophysis, adrenals** and **gonads.**

—P. M. N.

Influence of starvation on the growth and general physical development of children together with anatomical changes during inanition [Der Einfluss des Hungerns auf das Wachstum und die gesamte physische Entwicklung der Kinder (im Zusammenhang mit anatomischen Veränderungen beim Hungern)]. Stefko (W. H.), Ztschr. f. Konstit. (Berl.), 1923, **9**, 312-355.

Numerous tables and curves are produced as a result of a study of 800 children belonging to four different races. The author concludes that starvation causes marked growth changes in children at all ages, though all races are not influenced alike. The male is less stable than the female. These growth changes are in a great measure ascribed to effects on the incretory glands, since they undergo changes indicating pluriglandular insufficiency.—A. T. R.

Fructosediphosphatase in human organs (Fructosediphosphatase in menschlichen Organen. I.). Forrai (E.), Biochem. Ztschr. (Berl.), 1924, **145**, 47-53.

The presence of an enzyme capable of splitting fructosediphosphoric acid ester was found in the **testes, adrenals, thyroid** and **spleen.** Other organs of the body showed the same property.

—F. S. H.

Opotherapy by radiation (L'opothérapie par les radiations). Schmitt (C.), Bull. gén. de thérap. (Par.), 1923, **174**, 538-542.

Stimulative radiation of the **thymus** in a rachitic infant of 6 months was followed by improvement (doses of 3 minutes each at

intervals of 1 month). Three subjects with amenorrhea treated by monthly radiation of 5 minutes' duration over each **ovary** were brought to menstruation after a delay of from 8 days to 3 months. Precocious menopause (36-38-39-42 and 43 years) was similarly treated. Menstruation was regulated or reappeared and the nervous disturbances disappeared.—F. S. H.

Headache. Tierney (J. L.), Med. Clin. N. Am. (Phila.), 1924, **7**, 1515-1544.

Attacks of headache in women are most frequently associated with the menses, and are apt to cease during pregnancy, or with the menopause. Polyuria and bradycardia may occur with attacks of headache. Periodic temporary swelling associated with functional overactivity of the **pituitary** may explain attacks of migraine better than any other hypothesis. This view, however, seems paradoxical since during pregnancy there is freedom from attacks, although there is an associated pituitary hyperfunction. Moreover, the phenomena of migraine are commonly absent during the course of pituitary tumor. Migraine, with its vasomotor phenomena, is probably due to disturbed endocrine function, in which not only the pituitary, but probably the **thyroid** and **ovaries** are involved. Though the pituitary through its vegetative, nervous and vasomotor influence may play a rôle in the production of migraine, the latter must be differentiated from so-called pituitary headache which is a distinct entity. In the author's experience true migraine has been paroxysmal, usually hemicranial, constitutional, hereditary and ordinarily associated with visual disturbance, nausea and vomiting; cases of pituitary headache have commonly been found in individuals with other signs of pituitary disturbance, have been bilateral, non-paroxysmal, associated with different ocular manifestations, if any, and not usually accompanied by nausea and vomiting.—I. B.

Weight of ovaries with reference to other glands of internal secretion (thyroid, thymus, adrenals) and the uterus (Systematische Gewichtsuntersuchungen an Ovarien mit Berücksichtigung anderer Drüsen mit innerer Sekretion, sowie über ihre Beziehungen zum Uterus). Wehefritz (E.), Ztschr. f. Konstit. (Berl.), 1923, **9**, 161-171.

The study involves 730 ovaries, 655 uteri, 529 thyroids, 301 thymi and 701 adrenals from birth to 90 years of age. There were 45 cases of pregnancy from 19 to 46 years of age. The data are tabulated under eleven age groups. The ovaries, thyroid and adrenals during pregnancy average distinctly higher than in the non-pregnant, the ovaries and thyroid being more than 50% larger.—A. T. R.

Some phases of rejuvenation. Belfield (W. T.), J. Am. M. Ass. (Chicago), 1924, **82**, 1237-1242.

The rôle played by the gonads and the chromatin threads and chromosomes of the cell nucleus of sperm and ovum in the determination of sex is reviewed. Belfield states that in the number of chromosomes of the united sperm and ovum we recognize, not the immutable determination of the sex of the new being, but rather a distinct impulse toward the building of one or the other sex; an impulse that must seemingly be transmitted, as is the distinctive chromosomal structure, to every cell in the body; an impulse which early becomes manifest through the instrumentality of the endocrine glands, including the gonads. This recognition of the fertilized egg as the fundamental factor in sex is essential; it elucidates the otherwise puzzling fact that there is no group of sex features exclusively associated with **testis** or **ovary**; and other facts—including possibly homosexuality—inexplicable on the prevalent assumption that sex features emanate from gonads. Defective plans are sometimes manifest in structures deviating from the human type that cannot be explained by human embryology, but which are clearly features of earlier animals in the vertebrate phylum—the so-called arrests of phylogenetic development. The demonstrated difference in cell structure between male and female suggests the possibility that every cell in the body may contribute toward maleness or femaleness; as yet, however, only endocrine glands, including gonads, and cranial ganglions have been proved to make and unmake sex characters. Brown's work indicates that the function of the gonads requires integrity of certain ganglions at the base of the brain, which may be compressed through tumor formation of the **pituitary**; and that atrophy of the testes may be due to pressure on them rather than to pituitary disease. Among the organs which influence structure and function of the testes must be included certain ganglions at the base of the brain. On the traditional conception that sex emanates from testis or ovary is based the idea that the two sex complexes are essentially antagonistic and immutable. The biologic conception of sex is, on the contrary, not that it comprises two antagonistic entities, but rather that it is a single entity presenting various—and variable—degrees of femininity. There are known many instances in which the female—bird, quadruped or human—has matured normally, and later has assumed in marked degree the features and functions of the male; there is no instance known in which a mature male vertebrate has through intrinsic forces exhibited the corresponding change toward the female type; once a male, always a male; once a female, later a near-male, seems the natural course. Transmutation of females toward maleness, apparently anomalous, is such only in degree; for in all warm-blooded species the heavy burden of reproduction imposed on the female is transitory; and cessation of ovulation is often accompanied by some exchange of feminine for masculine features. Despite the

wealth of pertinent observations, clinical and experimental, the influence of gonads on sex characters is not yet exactly defined.

Homotransplantation of the human testis should, on biologic data, be more promising than that of the ovary; for these data indicate that the somatic tissues, inherited through the fertilized egg from the entire vertebrate phylum, are in harmony with the ancient maleness, but not with the new femaleness of the placental animals —that they are homologous with the testis but heterologous toward the ovary. And since, for the structure and maintenance of sex characters, somatic tissues—the endocrine organs, at least—are as essential as are the gonads, the male castrated before maturity may develop partial maleness, thanks to his somatic tissues, while the spayed young female lapses, thanks to those tissues, from femaleness toward maleness. Hence it seems possible, a priori, that a testis transplanted into an otherwise normal young man deprived of the testes might reinforce the maleness of the host's somatic tissues, even though the ovarian transplant into the female fails to do so. Belfield asserts that Steinach's method of rejuvenation merits little attention, for it is founded on error and refuted by experience. Steinach's theory of rejuvenation, for men at least, falls to the ground. The experimental work of careful investigators on rejuvenation by testis implantation seems to have established these results on animals: Testis transplantation succeeds often in young, rarely in old, animals; success meaning merely the maintenance of vitality for a period of months. Though the transplant never produces sperms in its new host, it may function to the extent of preserving the masculinity of a castrated young male for a limited time, or of causing in a spayed young female hypertrophy of the clitoris and distinctly masculine behavior. The life of the transplant is much shorter than that of the native testis; within a few months its elements are replaced by connective tissue, and its physiologic effect on its host ceases. Stimulation of erection sometimes follows testis transplantation in old men, appearing within a few hours and ceasing within a few days. This is apparently the effect of pre-formed substances contained in the transplant and absorbed therefrom by the host's tissues. Similar effects have followed the injection of milk. A lasting recovery of lost erectile power in old men through testis transplantation is yet to be demonstrated. The future of testis therapy seems to depend on the isolation of the activating substance produced in the testis corresponding to **thyroxin** or **insulin.** . Until this shall be accomplished, the injection of an emulsion of testis tissue seems the most promising form, though such a mixture of unknown proteins must be a tentative remedy. It seems probable that gonad therapy, begun as an irrational attempt at an impossible "rejuvenation," may emerge from the disrepute of its infancy and develop into a valuable means for relieving ailments that are not now associated with gonad deficiency; for it is demonstrated that the gonad does

not originate sex; that it is less essential to the maintenance of sex than is the thyroid or the suprarenal; and that it is indeed one of a chain of interacting endocrine glands, efficiency in every link of which is essential to normal function, sexual or somatic.—Courtesy Am. M. Ass.

Action of x-rays on the testicle of the cock (Action des rayons X sur le testicle du coq). Benoît (J.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 802-805.

The total disappearance of the seminal cells under the influence of x-rays does not prevent the development of the comb. This sexual character is developed under the influence of the testicular hormone.
—T. C. B.

Menstruation and lactation. A clinical statistical study (Menstruations et allaitement. Observations cliniques-statistiques). Canelli (A. F.), Nourrisson (Par.), 1924, **12**, 92-100.

Twenty-five per cent of the nursing mothers menstruated during lactation. The mean duration of lactation before menstruation reappeared was 4 months and a half. Precocity in this was exhibited in the primaparas. In 90% of the cases the duration of each period was the same as that before pregnancy. In 30% of the cases the periods occurred in regular sequence. Thirty per cent of the nurslings of the menstruating mothers lost weight during the periods, and 17% showed diarrhea.—F. S. H.

Vaginal rhythm in the hedgehog; effect of injecting follicular liquid (Le rythme vaginal du hérisson; action de l'injection de liquide folliculaire). Courrier (R.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 808-809.

Injection of follicular liquid into a hibernating hedgehog provokes vaginal modifications characteristic of sexual activity.
—T. C. B.

Relation between the corpus luteum and menstruation (Sur les rapports du corps jaune et de la menstruation). Cotte (G.), Gynéc. et Obst. (Par.), 1923, **8**, 517-527.

Report of a series of observations on the histological character of ovaries removed from women at different periods of the menstrual cycle. The results lead the author to believe that the corpus luteum does not play a preponderant rôle in the initiation of the menses, and that if a secretory factor is at work, it probably takes its origin from the different ovarian elements. Moreover, it frequently happened that shortly after the removal of an ovary with a ripe follicle menstruation appeared. An inhibitory effect of the structure is implied by these results.—F. S. H.

The endocrine gland of the deferential ampulla in the horse, ass and mule (La glandola endocrina dell' ampolla deferenziale degli equidi). Cutore (G.), Arch. ital. di anat. e di embriol. (Firenze), 1922, **19**, 79-94.

There is an interstitial gland in the deferential ampulla of these domestic animals, but it is more developed in the mule than in the horse and ass. Probably this has a slight effect on the secondary sexual characters.—P. M. N.

Preparation and properties of an ovarian hormone. Doisy (E. A.), Allen (E.), Ralls (J. O.) & Johnston (C. S.), J. Biol. Chem. Balt.), 1924, **59**, xliii-xliv.

A hormone which causes typical estrus in spayed rats has been prepared from liquor folliculi and whole ovaries. The method is given briefly. The hormone is not cholesterol. It is soluble in lipoid solvents but insoluble in water. It is stable towards dilute boiling acids and alkali. Dissolved in oil its activity is not destroyed by autoclaving at 15 pounds for 15 minutes. Preparations from **placenta**, liquor folliculi, and ovaries from which the liquor folliculi have been removed are active; those from embryos and **corpora lutea**, negative.—F. S. H.

Physiology of Bidder's organ and experimental-physiological sex reversal of male toads to females (Untersuchungen über das Biddersche Organ der männlichen und weiblichen Kröten. II. Mitteilung: Die Physiologie des Bidderschen Organs und die experimentell-physiologische Umdifferenzierung von Männchen in Weibchen). Harms (W.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1923, **69**, 598-629.

The protocol is given of 49 extirpation experiments involving the **testis** and **ovary** with and without Bidder's organ. Harms concludes that Bidder's organ of the adult male toad represents a rudimentary ovary-like gonad, with oocytes which mature only as far as the synaptic stage when they degenerate. Or this structure may be viewed as a primitive gonad of the urodele stage of the toad. If the testes of adult toads are removed, the secondary sex characteristics are retained, due to the influence of a male incretion from Bidder's organ. With removal of the inhibitory influence of the testis and over-feeding with fatty foods and lecithin, there is hypertrophy of some of the cells in Bidder's organ till they apparently become normal egg cells. To the extent that this organ changes to an ovary the latent female characteristics develop, i. e., uterine tube and uterus develop and the physical features and behavior become feminine while the male characteristics diminish. Possibly metabolism thus plays an important rôle in the normal differentiation of the sexes in amphibia. Some literature is cited.—A. T. R.

Basal metabolism in insufficiency of the testes, with or without feminism (Le métabolisme basal dans l'insuffisance testiculaire avec ou sans féminisme). Harvier (P.) & Van Bogaërt (L.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 672-673.

The basal metabolism is diminished in testicular insufficiency, but approaches the normal when the genital atrophy is accompanied by heterosexual morphology.—T. C. B.

Corpus luteum of the salamander [Das Corpus luteum des Molches (Triton vulgaris)]. Hett (J.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1923, **68**, 243-271.

Description of the changes in the ruptured follicular wall and the formation of a rudimentary corpus luteum, which is similar to the corpus luteum of the fowl.—A. T. R.

Bidder's organ in the frog (Das Biddersche Organ von Bufo vulg. Laur.). Hoepke (H.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1923, **68**, 491-513.

Hoepke concludes from extirpation experiments that Bidder's organ produces an incretion which is useful in the metabolism of the entire body and which cannot in general be dispensed with without damage; but it has no specific action on the secondary sex characters. Some literature is cited.—A. T. R.

Sterility: A study based on a series of 526 patients. Hunner (G. L.) & Wharton (L. R.), South. M. J. (Birmingham), 1924, **17**, 269-275.

The authors state that our knowledge of the endocrine aspects of this subject is very meager and they condemn strongly the present tendency to use polyglandular therapy in combating it.—J. C. D.

Case of precocious puberty. Hutchison (R.), Proc. Roy. Soc. Med. (Lond.), 1924, **17**, 8-9 (Sect. Dis. Child.).

The case is reported of a girl aged 3½ years who began to menstruate at 17 months and continued at more or less regular intervals of one month up to the present time. The child's weight is 52 pounds, height 44 inches, and the secondary sexual characteristics are well developed. Though dentition is normal, the skeletal development is that of a child of 13 or 14 years of age. Aside from fits of bad temper, the child is mentally normal and bright for her age. The condition is believed to be due to ovarian hypersecretion.
—I. B.

Interstitial tissue of the testis of domestic mammals (Das Hodenzwischengewebe der Haussäugetiere). Lenninger (W.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1923, **68**, 230-242.

From an examination of the testes of the horse, cattle, sheep, goat, pig, dog, cat, deer and chamois, Lenninger concluded that the size and number of interstitial cells is not proportional to the prominence of the secondary sex characters. In the deer they increase before and during rut, while after rutting there is an increase in connective tissue. Albuminous crystals could be demonstrated in the intertubular tissue only in the deer preceding rutting.—A. T. R.

The effect of corpus luteum on behavior of rats. Macht (D. I.) & Seago (Dorothy W.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 255.

Female white rats tested in a maze responded by an increase in muscular and cerebro-spinal efficiency to injections of corpus luteum and whole **ovary.** Spayed animals reacted as did normal rats. The effects appeared 15 minutes after injection and lasted 24 hours.—J. C. D.

The scrotum as a temperature regulator for the testes. Moore (C. R.) & Quick (W. J.), Am. J. Physiol. (Balt.), 1924, **68**, 70-79.

In the rat at a room temperature of 14° C. there may be a difference of 7.5° C. between the peritoneal cavity and the scrotum. Evidence is given that the scrotum is a thermo-regulator for the testes.—T. C. B.

Changes in the follicular wall after its rupture in the ovary of the domestic hen (Die Veränderungen der Follikelhüllen beim Haushuhn nach dem Follikelsprung). Novak (J.) & Duschak (F.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1923, **69**, 483-492.

A description of the formation of a rudimentary **corpus luteum** from follicular epithelium and theca interna and then its degeneration similar to that which occurs in mammals.—A. T. R.

Racial modifications by ovarian grafts in the cock (Modifications raciales par greffe ovarienne chez les coqs). Pézard (A.), Sand (K.) & Caridoit (F.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 623-625.

In two cases the transplantation into the cock, castrated or not, of an ovary of a hen of a different race provoked a sexual inversion of plumage and the appearance of new pigmentary characters.
—T. C. B.

Cerebral obesity and genital atrophy. Raab (W.), Wien. Arch. f. inn. Med., 1924, **7**, 443-531.

Raab observed 43 patients with cephalic obesity or hypogenitalism. He prefers this term to dystrophia adiposogenitalis because he believes, with Biedl, that the symptoms may be caused either by an

affection of the **pituitary** gland, or of the brain centers, or of the communication between them. The height of the dorsum sellae in some patients might speak for the latter possibility. In one case the pituitary gland seemed to be the only organ affected. Dystrophia adiposogenitalis is not a uniform syndrome. Each of its component elements may occur isolated. It seems that the centers for the genital organs are on the floor of the third ventricle, nearer to the pituitary gland, while the obesity depends on centers in the tuber cinereum near the mammillary bodies.—J. Am. M. Ass., **82**, 1486.

Transplantation of testes from the chimpanzee (Structure des testicules d'un chimpanzé et résultats physiologiques de leur greffe). Retterer (E.) & Voronoff (S.), J. d'urol. (Par.), 1923, **15**, 417-430; abst., Ber. ü. d. ges. Physiol. (Berl.), 1924, **22**, 192.

The testes of a healthy 5 or 6 year old chimpanzee were grafted into two men. The left testis was implanted in a man 52 years old who was in a generally run-down condition, with loss of memory, obesity and impotence. After 3 months the patient had lost 7 kilograms and strength and memory had improved. At the present time, 7 months after the operation, this man gives an amazing impression of youth and strength. The genital function has been completely restored. The right testis of the chimpanzee was engrafted in the other patient 6 months later and up to this time there have been no definite results.—M. D. G.

Hermaphroditismus verus in the human being (Ein Fall von Hermaphroditismus verus beim Menschen). Schauerte (O.), Ztschr. f. Konstit. (Berl.), 1923, **9**, 373-384.

A 16-year-old twin girl is described who had a fair-sized penis that showed erectile power at the age of 10, a scrotum on one side but also a vulva into which opened the urinary passage. She had many boyish traits during childhood. The breasts enlarged at 14 years and menstruation commenced when 15½ years and remained regular. Laparotomy revealed a normal uterus, one enlarged **ovary** containing a blood cyst and a normal uterine tube. Section of the scrotal contents proved them to contain a true **testis** with spermatogenesis going on as far as spermatids. Between the tubules was an abundance of **interstitial cells.** By the side of each testis was a functioning ovary with ovarian follicles, ova and **corpora lutea.** Section of the amputated penis showed well-developed corpora cavernosa. After removal of the ovotestis, menstruation continued and the sex inclination of the patient reversed to the feminine side.

—A. T. R.

Testes transplantation. Sechi (E.), Riv. di biol., 1923, **5**, 329-346; abst., Ber. ü. d. ges. Physiol. (Berl.), 1924, **23**, 114.

The consequences of castration and the effects of transplantation of testes is reviewed. The investigator next reported his experiments on rabbits aged 3 months to 3 years. An autoplastic or homoplastic transplantation was performed and the testes observed histologically after a period of 12 days to 3 months. In 17 cases the testes were resorbed or replaced by connective tissue. In 1 case it degenerated, in 5 cases the interstitial tissue remained, and in 2 instances the Sertoli cells were found in the tubules. A definite conclusion concerning the incretory function of the interstitial tissue or the Sertoli elements cannot be derived from these experiments.
—M. D. G.

Pregnancy after bilateral amputation of the mammae (Schwangerschaft nach doppelsetiger Mammaamputation). Schneider (G. H.), Monatschr. f. Geburtsh. u. Gynäk. (Berl.), 1923, **64**, 295-296.

Evidence is presented from this case report that the internal secretory function of the mammae (if such exists) is not concerned in uterine involution after pregnancy or in **ovulation**, since both these processes took their normal course in this breastless woman.
—F. S. H.

The effect of pubescence, menstruation and menopause on the voluntary activity in the albino rat. Slonaker (J. R.), Am. J. Physiol. (Balt.), 1924, **68**, 294-315.

There is a marked rhythmic increase in voluntary activity during the sexual life of isolated female rats which is not seen in the male. This rhythm is not manifested before puberty nor after the menopause.—T. C. B.

The awaking of the copulatory ability in the male albino rat. Stone (C. P.), Am. J. Physiol. (Balt.), 1924, **68**, 407-424.

Stone studied the age at which albino rats, raised under optimum conditions, developed copulatory ability, and correlated this with the maturation of spermatozoa and the development of the organs of intromission. The ages ranged from 37 to 72 days, with a mean of 48 days. One-third of the group copulated before the age of 43 days. Nineteen of 56 males copulated before mature spermatozoa were found in the seminal tubules.—T. C. B.

A methylating function of the thyroid, and biological significance of iodine (Ueber eine Methylierungsfunktion der Schilddrüse, zugleich ein Beitrag zur biologischen Bedeutung des Jods). Stuber (B.), Russman (A.) & Proebsting (E. A.), Biochem. Ztschr. (Berl.), 1923, **143**, 221-235.

An ingenious series of experiments on rabbits in which it was apparently found that the injection of guanidine acetate is followed by an increase in blood creatinine and creatine. The reaction does

not occur in thyroidectomized animals unless thyroid substance or iodine is fed. This is interpreted as indicating a methylating function of the thyroid and iodine.—F. S. H.

The gonads and carbohydrate metabolism (Beiträge zur Kenntnis der inneren Sekretion der Keimdrüsen. I. Mitt. Keimdrüsen und Kohlehydratstoffwechsel). Tsubura (S.), Biochem. Ztschr. (Berl.), 1923, **143**, 248-290.

Experiments were performed on rabbits. It was found that the fasting value of the blood sugar was not markedly altered by castration. On the other hand, castration of sexually mature animals was followed by a lowering of the alimentary and parenteral sugar tolerance which became manifest some three weeks after the operation and lasted for a long time. Unilateral tying off of the spermatic cord and simultaneous extirpation of the **testis** of the other side was also followed by a lowering of alimentary sugar tolerance in the sexually mature animal. The same phenomenon appeared after bilateral tying off of the spermatic cord. Radiation of the testes produced the same reaction. Both tying off and radiation produce a high grade of disturbance of the spermatic elements while the Sertoli cells remain intact. From this it appears as if the spermatic elements play a significant rôle in carbohydrate metabolism. The lowered sugar tolerance can be raised by transplantation of testes, but the effect does not last very long. Neither feeding of gonadal substance nor injection of testicular extract has any effect upon sugar tolerance. Apparently glycogen formation from sugar mobilization from glycogen in the liver is less rapid in castrated animals than in the controls. No change in the amount of blood amylase is to be found after castration. Castrated males react as do castrated females to **adrenalin** with marked hyperglycemia. When diuretin is injected into castrated rabbits more marked hyperglycemia is produced than in the controls. The same is true of **pituitrin. Thyroid** feeding produces no significant change in the blood sugar of normal or castrated rabbits. It does produce, however, in normal rabbits a lowered sugar tolerance and in the castrates an increased tolerance. The kidneys appear to be more permeable to sugar after castration. Phenolsulphonephthalein excretion is delayed. Many changes occur in the other incretory organs after castration.

—F. S. H.

Gonads and respiratory exchange (Beiträge zur Kenntnis der inneren Sekretion der Keimdrüsen. II. Mitt. Keimdrüsen und respiratorischer Gaswechsel). Tsubura (S.), Biochem. Ztschr. (Berl.), 1923, **143**, 291-322.

Tsubura finds that a diminution of respiratory exchange follows gonadectomy in both sexes. Unilateral tying off of the spermatic cord and removal of the **testis** of the other side produces a lowering

after some months. It is apparent that this phase of metabolism is in some way related to the spermatogenous elements of the testicles. The lowered gas metabolism is raised somewhat by implantation of the gonads. Feeding testicular substance had no effect. Thyroid feeding stimulates gas exchange in castrated as well as in normal animals.—F. S. H.

The histologic and physiologic investigation of the so-called phenomenon of rejuvenation (Beitrag zur histologisch-physiologischen Erforschung der sogenannten Erscheinungen der Verjüngung. 2. vorl. Mitt.). Wilhelm (O.), Rev. med. de Chile (Sant. de Chile), 1923, **51**, no. 7-8; abst., Ber. ü. d. ges. Physiol. (Berl.), 1924, **23**, 261.

Additional communication on an experiment which has previously been reported. A number of new experiments were carried out on dogs. In an 18-year-old dog there was restoration of the sexual function and remarkable improvement in general condition with unusual increase in weight after unilateral ligation and resection of the epididymis. About 10 months after the operation there was a loss of weight—as much as had been gained immediately following the operation. The sexual power, however, was retained for some time. Some months later a stubborn itch developed; death occurred 1½ years after the operation. The case of an 11-year-old bulldog with unilateral resection of the epididymis is described in detail. The potence was increased, reaching a maximum 6 months after the operation. Then rapid decline took place. Other dogs with unilateral or bilateral ligation and resection of the epididymis were observed. In 4 dogs there were pronounced positive results, bodily as well as psycho-sexual. One animal, in which an epithelioma was also removed, died suddenly 2 months after the operation. A second dog was killed 5 months after the operation for the purpose of histological investigation. The weight had increased from 34 to 44 kg.; complete psycho-sexual regeneration had taken place; there was return of sexual potence and a change in the general condition occurred a short time after the operation. Four months after operation in a third dog there was increase in weight from 16 to 21 kg., rejuvenation of the skin, reduction of the arcus senilis, and extensive changes in the psycho-sexual state. A fourth animal was observed 4 months after operation. There was increase in weight from 18 to 30 kg., complete rejuvenation of the hair and marked change in the general condition. The observations on the third and fourth animals were continued. In a fifth dog the results were negative. It is worthy of note that the operation disclosed an inflammatory change in the subcutaneous tissue and adhesions over the entire extent of the tunica vaginalis and albuginea. In 3 cases of homotransplantation in old dogs (subcutaneous, intramuscular, and intratesticular) the following results were obtained: (1) Sub-

cutaneous transplantation brought about positive results; after subsidence of the positive results, 2 years later, a second transplantation (intratesticular) was performed, but the results were negative. (2) Intramuscular and intratesticular transplantation was performed. The weight increased from 6 to 11½ kg. (The animal was well fed for one month before the operation and the increase in weight was sudden.) Return of sexual potence was noted; he became very aggressive. There was partial rejuvenation of the skin. The animal was in excellent general condition. There was partial disappearance of the arcus senilis. Three and a half months after the operation a decline set in. (3) Intramuscular transplantation was performed. Two and a half months after the operation the dog died suddenly, although potence had returned and the animal seemed more active. There are no definite data concerning the condition of the transplant; gradual resorption probably took place. Further data are reported regarding a previously mentioned patient, operated upon at the age of 62 years (unilateral ligation and resection of the head of the epididymis). There was an extraordinary recovery from angina pectoris; the attacks ceased entirely. A year later there was a return of the phenomenon, successfully treated, however, with testicular extract. In another patient, operated upon at the same time for hernia, there was return of potence and decided improvement in the general condition. The paper includes many splendid photographs of the experimental dogs.—M. D. G.

The induction of labor by quinine and pituitrin. Browne (F. J.), Edinb. M. J., 1924, **31**, 25-33.

The author considers that the particular value of this method lies in avoiding the danger of infection, which accompanies the induction of labor by mechanical means.—J. C. D.

A child with congenital syphilis and diabetes insipidus presenting the syndrome of corpora striata lesion. Dwyer (H. L.), Med. Clin. N. Am. (Phila.), 1924, **7**, 1201-1204.

The patient is a girl of 8 who came to the hospital 8 months before, complaining of intense thirst and polyuria. After admission, her clinical picture entirely changed, presenting motor disturbances, general muscular rigidity, mask-like facial expression, and tremor. Following antisyphilitic medication the symptoms of diabetes insipidus improved, but the nervous symptoms became intensified.—I. B.

Pituitary tumor. Engelbach (W.), Med. Clin. N. Am. (Phila.), 1924, **7**, 1365-1400.

In a series of 375 uncomplicated pituitary disorders, tumor was the cause in only 13 cases. The re-analysis of these cases, some of which have been under personal observance for from 1-10 years,

presented many points incongruous with the present-day teaching. The general hormonic signs are very much more dependable for the diagnosis of secretory disturbances of the hypophysis than the neighborhood and general intracranial symptoms. In one of the 13 cases there was a marked response to specific treatment following simple temporal decompression operation, the patient regaining complete normal vision after having had for a number of months homonymous hemianopsia and incipient optic atrophy. Another luetic case had as its chief complaint glycosuria, which responded temporarily to anti-luetic treatment. In 3 of these cases having a luetic etiology there was absence of an abnormally enlarged sella.

The symptomatology can be readily subdivided into: (1) those symptoms produced by intracranial pressure, and (II) those due to the effect of the hormones of the hypophysis upon other structures and distant organs of the body. (I) The intracranial pressure symptoms can again be subdivided into: (1) neighborhood or localized signs, due to pressure upon the tissues in the region of the pituitary gland, and (2) general intracranial pressure symptoms resulting from increased pressure within the cranium. (II) The hormonic signs are grouped into: (1) general hormonic signs, affecting the individual as a whole, such as height, weight, proportions, adiposity, pigmentations, hair, growth, etc.; (2) regional hormonic signs, which are the changes in local or limited portions of the body, as of the nose, lips, teeth, mammae, genitalia, fingers, toes, etc.; and (3) laboratory signs, which are really a part of the general hormonic signs, but are classed under a different heading on account of the special technic required for their identification. These laboratory signs consist of changes in the basal metabolism and blood chemistry and the effects of the injection of various pituitary substance upon the blood pressure, pulse rate, color, involuntary muscle contractions, urinary output, etc. Pituitary tumors can and occasionally do exist without modifying the size and shape of the sella. In 4 of 13 cases there was no definite enlargement of the sella turcica, and in 3 there was absolutely no enlargement or erosion of any part of the sella portrayed by the radiogram. In some of the others a normal sella for a considerable length of time was demonstrated. Sooner or later, in the majority, erosion of either of the processes or enlargement of the sella occurred. The next most abused neighborhood signs with regard to importance in the diagnosis of pituitary tumor are the ocular signs. A transient, fleeting blindness, asymmetric and varying in its location, is the more constant ocular sign of these tumors. This retinal blindness is due to direct or dragging pressure upon the chiasm or the optic tract just posterior to the chiasm. The amount of retina involved depends upon the location of the pressure, and, in consequence, upon the direction of the growth of the tumor. The amount of blindness may be very small, or may involve the complete half of the eye, or the entire optic tract

may be involved with homonymous hemianopsia, with nasal blindness in one eye and temporal blindness in the other. As the tumor grows, it sometimes decompresses the anterior wall of the sella (the posterior wall of the sphenoid cells) or breaks through the posterior clinoid process. When this self-decompression occurs, the pressure is temporarily relieved from various portions of the optic chiasm, allowing the sight to return to the retina supplied by those fibers. This accounts for the very peculiar relief from or change in the eye symptoms of the patient. Pituitary headache is probably due to direct pressure upon the capsule of the gland and the intracranial pressure. The patient frequently complains of pain directly in the eyes or eye having perimeter deviation. In two cases, which lasted six months to one and one-half years, respectively, both with unquestionable enlargement of the sella and perimeter signs, with general hormonic signs of pituitarism, there was and had been no headache. In all but one case there were outspoken, general hormonic symptoms and signs—objective changes in the osseous system, localized adiposity (such as the girdle adiposity characteristic particularly of pituitary disorder), polyuria, complete and prolonged amenorrhea and pigmentation, each of which is specifically connected with pituitary disorder. Six subjects had polyuria, and 3 glycosuria. In all cases it was considered a hypophyseal glycosuria on account of its peculiar dissociation from carbohydrate intake and hyperglycemia. In some of these cases the blood sugar was very high, with a normal urine, and in other cases the blood sugar was apparently normal, as in renal diabetes, with variable glycosuria. Classical pituitary adiposity was present in 4 cases, and in 1 case pituitary hibernation occurred.

Of these 13 subjects, with an average duration of 5½ years, only 3 died. Of the other 10 patients, still living, the duration varied from 1-14 years, and these have been under more or less constant observation. Of these, 2 have been operated upon and a number of others have been advised to have operation, on account of the positive signs of progress of the tumor growth, but have not accepted surgical treatment. A number have been advised against operation on account of the presence of definite symptomatology indicating absence of progression or even regression in size of the neoplasm, as proved by the subsidence of both neighborhood and general intracranial pressure symptoms.

The indications for treatment depend upon the progression of the tumor at the time of observation. If there is evidence of a tumor which has become stationary, as occurs in some of these cases, particularly cyst of the hypophysis, there is no indication for immediate surgical intervention. On the other hand, the treatment for rapidly growing tumor, which shows progressive ocular or sellar signs and evidence of increasing intracranial pressure, should be considered surgical. Possibly one exception to this rule would

be those cases giving an unquestionable specific history with positive physical and laboratory reactions. These subjects might be treated for a limited length of time on specific and x-ray treatment, on the basis of the possibility that the neoplasm is due to gumma of the hypophysis. If this treatment is not effective in the course of 6 or 8 weeks, it would be well to consider surgical intervention. In patients presenting evidence of rapid progression, who do not accept an operation, the only other means of treatment is x-ray and radium. In these cases radium is not very efficient on account of lack of deep penetration. High voltage x-ray treatment, focused upon the hypophysis through the temporal and frontal regions, beneath the hairline, has been effective in the hands of some men, mostly of the foreign schools. With regard to the medical treatment, it has practically no field in these cases, except in a minor secondary rôle in those which have as a result of pituitary tumor a hyposecretion of one or both lobes. Substitution of these preparations to relieve the secondary hormonic signs, such as polyuria, obesity, amenorrhea, hibernation, pituitary headache, etc., may be given. It should always be borne in mind, however, that there is a very slight possibility of activating the pituitary tumor by giving these substances, and for this reason their effect should be observed very carefully, and at any signs or symptoms of hypersecretion this medication should be discontinued.—I. B.

Surgery of pituitary body. Frazier (C. H.), Arch. Surg. (Chicago), 1924, **8**, 39-61.

Frazier analyzes 18 cases, representing what were regarded as primary intrasellar lesions, for the relief of which a transsphenoidal hypophysectomy was performed. In this series, there were no operative fatalities. Three patients have died in the interim, and in the other cases the results have been satisfactory in 75%. The relative merits of glandular therapy, irradiation and operation are presented. The indications for operation are clearly set forth. Surgical intervention offers an assurance not only of the arrest of visual deterioration, but also of improvement in a considerable proportion of cases. The combination of operation and irradiation will prolong the period of relief or prevent recurrence. The transsphenoidal operation is devoid of serious risk.—J. Am. M. Ass., **82**, 822.

Action of pituitary extract on renal function (Uber die Wirkung der Hypophysenextrakte auf die Nierenfunktion). Fromherz (K.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1923, **100**, 1-37.

This paper forms an important contribution to our knowledge of the action of pituitary extract on renal secretion. Until now two effects, apparently contradictory, have been described. An injection of the extract made intravenously into the anesthetized animal

causes diuresis. An injection made subcutaneously into the normal animal has an antidiuretic effect in that it delays the excretion of a volume of water taken by mouth; in this connection there is, moreover, the well-known use of the extract to counteract **diabetes insipidus.** Fromherz now shows that both effects can be obtained either in the normal or in the anesthetized animal. Using dogs from which the urine is collected 2-hourly by catheter, simultaneous subcutaneous injection of pituitary extract and oral administration of water is followed by suppression of urine formation lasting for 6 or 7 hours. If, however, the injection of pituitary extract be intravenous, or, being subcutaneous, precedes the administration of water by 1 hour, there is not only no suppression of urine, but a positive diuresis is observed. Similarly in the anesthetized rabbit a single injection of pituitary extract causes diuresis; if the same dose be slowly infused into the vein diluted in a large volume of the same saline, there is a suppression of the outflow from the ureters so long as the infusion lasts (for example, 1 hour). Fromherz considers that in every case pituitary extract has an antidiuretic effect, sooner or later giving way to a diuretic action. Under some conditions only one of these is observed, while the other escapes notice. He confirms the statement that the concentration of chlorides in the urine is greater while pituitary extract exerts its effect; this effect is primarily renal; changes in the blood (dilution) are secondary.—Physiol. Abst., **9**, 23.

Basal metabolism in the non-hypophyseal adiposo-genital syndrome (Le metabolisme basal dans le syndrome adiposo-génital non hypophysaire). Labbé (M.) Stévenin (H.) & van Bogaert (L.). Ann. de méd. (Par.), 1924, **15**, 112-118.

A study of basal metabolism in 10 cases of adiposity combined with genital insufficiency gave 5 well below normal, 2 slightly below and 3 within normal limits.—F. S. H.

The glucose equivalent of insulin in depancreatized dogs. Allan (F. N.), J. Biol. Chem. (Balt.), 1924, **59**, xxviii.

The glucose equivalent of insulin falls off with increasing dosage of the hormone.—F. S. H.

Experimental studies in diabetes. Series V. Acidosis. I. The production of diabetic acidosis and coma in dogs. Allen (F. M.), J. Metab. Res. (Morristown), 1923, **3**, 775-795.

The less frequent occurrence of acidosis and coma in dogs with experimental diabetes has been advanced by some workers as an argument against the identity of this form of diabetes and that spontaneously occurring in man. In the present paper Allen presents the protocols of 4 partially depancreatized dogs, all of which developed this complication. Two showed fasting acidosis, whereas

the others developed it on excessively high fat diets. The author concludes from this that clinical diabetes is in no detail different from this form of experimental diabetes. Totally depancreatized dogs did not develop coma, most probably because in them fat digestion and absorption are practically absent.—I. M.

Experimental studies in diabetes. Series V. Acidosis. II. Fat intoxication. Allen (F. M.), J. Metab. Res. (Morristown), 1923, **3**, 797-813.

The author refers to his previous observation of a form of intoxication which he believes to be due to the fat in the diet. In the present paper the protocols of 7 dogs showing signs of "fat intoxication" are reproduced. The condition is brought about by prolonged use of diets excessively rich in fat. The first symptoms are indigestion, refusal of food even when starving, loss of hair with eruption of the skin, various grades of atonia and muscular incoordination and twitching and at times convulsions. This is independent of both acidosis and diabetes. No organic lesions are found in the central nervous system or viscera. The author considers this an additional argument against the use of high fat diets in diabetes.—I. M.

Severe infantile diabetes treated successfully with insulin (Diabètes infantiles graves traités avec succès par l' insuline). Apert (E.), Bull. et mém. Soc. méd. d. hop. de Par., 1923, **47**, 1552-1563.

Detailed report of the results of insulin administration to several diabetic children. Beneficial effects were observed. The use of insulin in severe diabetes attended by emaciation and acetonuria is advocated, but its general use in the benign types susceptible of amelioration by dietary procedures is condemned.—F. S. H.

The absence of effect of insulin on the heat production in isolated frog's muscle. Azuma (R.) & Hartree (W.), Biochem. J. (Lond.), 1923, **17**, 875-877,

Experiments have been performed on the sartorius muscle of Rana temp. comparing (a) the magnitude of the initial anaerobic heat production, and (b) the magnitude and course of the oxidative recovery heat production before and after subjection to a high concentration of insulin. No change whatever has been found in either case. The injection of insulin into the intact frog, on the other hand, was shown to produce a well defined effect. It is clear, therefore, that the action of insulin does not reside in any effect on the muscle.—F. S. H.

Factors influencing the production of insulin. Banting (F. C.) & Gairns (S.), Am. J. Physiol. (Balt.), 1924, **68**, 24-30.

There is a continual secretion of insulin, because when the

islet cells are removed the blood sugar is gradually increased. Increase of blood sugar stimulates the islet cells to produce an adequate amount of insulin to reduce the sugar to normal. The secretion of insulin is not necessarily dependent on a nerve supply.
—T. C. B.

Insulin in tissues other than the pancreas. Best (C. H.), Smith (R. G.) & Scott (D. A.), J. Biol. Chem. (Balt.), 1924, **59**, xxx-xxxi,

Insulin is present in reduced amounts in the tissue of completely diabetic dogs, to an amount more than half that present in tissue of normal dogs. Obviously, the insulin must exist in diabetic tissues in a comparatively unavailable form. The results indicate that all the muscle tissue contains at least 20 times as much insulin as the total weight of the pancreas. The blood contains about five times as much. The liver may contain an equal amount. The active blood sugar reducing principle was extracted from the brain, submaxillary, **thyroid, thymus,** heart muscle, lung, **spleen,** bone and skeleton muscle. The tissues of animals which have been subjected to ether anesthesia seems to contain much less insulin than normal or diabetic tissue.—F. S. H.

The effect of high fat feeding in diabetes. Black (D. R.), Med. Clin. N. Am. (Phila.), 1924, **7**, 1127-1136.

Black concludes that those patients who fail to respond to protein meals with elevated blood sugar curves apparently have no difficulty in maintaining a normal nitrogen balance. They do not tolerate even a moderate amount of fat. Those who respond to protein meals with a definite elevation of blood sugar are prone to burn their body protein. They tolerate diets relatively high in fat, although in this some have failed to exceed to any appreciable degree fat rations in excess of that calculated from Woodyatt's formula. The apex of the sugar curve following protein meals is delayed usually to the third hour, unlike the glucose tolerance curve in which the apex occurs during the first hour.—I. B.

Some effects of insulin on the carbohydrate and phosphorus metabolism of normal individuals. Blatherwick (N. R.), Bell (M.) & Hill (E.), J. Biol. Chem. (Balt.), 1924, **59**, xxxv.

When 40 rabbit units of insulin are given before the glucose there is usually a marked drop in plasma phosphate and in the excretion of the urinary phosphorus at the time of hypoglycemia. In some cases the plasma phosphate may first increase and then decrease. The fermentable sugar of the urine decreased by 12 and 28 per cent when insulin was given.—F. S. H.

Some factors influencing the response of rabbits to insulin. Blatherwick (N. R.), Long (M. L.), Bell (M.), Maxwell (L. C.) & Hill (E.), J. Biol. Chem. (Balt.), 1924, **59**, xxxvi.

Rabbits fed a low carbohydrate base-forming diet are less resistant to insulin than those fed a high carbohydrate acid-forming diet. This is probably not due to glycogen in the tissues. "Education" to insulin convulsions is producible. Data are given which support the hypothesis that the dosage of insulin varies directly with the body weight and not as the square of the weight. Growing rabbits must be gaining steadily in order to give good results with insulin. The animals are used every 7th day. Rabbits which have never received insulin are given sufficient amounts to produce convulsions before they are used for standardization.—F. S. H.

A study of the reaction of normal human subjects to intravenous injections of insulin. Bodansky (A.) & Simpson (S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 280.

The blood sugar curve showed a minimum 18 minutes following injection with return to normal at the end of an hour. In overweight subjects the reaction is not so great but recovery is slower. "It is suggested that varying degrees of adiposity as such underlie the differences in the reaction to insulin of animals used in its assay."—J. C. D.

Influence of insulin on the disturbances of the menstrual function in a case of severe diabetes (Influence de l'insuline sur les troubles de la fonction menstruelle dans un cas de diabète grave) Carrasco Formiguera (R.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 826-827.

In a patient with amenorrhea and diabetes the menstrual periods were restored after treatment with insulin.—T. C. B.

Blood concentration in insulin hypoglycemia. Drabkin (D. L.), Page (J. H.) & Edwards (D. J.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 309-311.

Dogs were anesthetized with iso-ethyl-barbituric acid, a drug which does not influence the blood sugar or blood concentration. After large doses of insulin, 20 units per kilo, there was an increased concentration of the blood accompanying the hypoglycemia. —J. C. D.

Further purification of insulin and analysis of the product. Doisy (E. A.) & Weber (C. J.), J. Biol. Chem. (Balt.), 1924, **59**, xxxiv-xxxv.

Fractionation of crude insulin employing alcohol as the solvent and the phenomenon of isoelectric precipitation have yielded a

product which lies between 0.015 and 0.025mg. per Toronto unit. This purified insulin gives the biuret reaction corresponding to an equivalent weight of peptone. The total nitrogen is 14%. After hydrolysis the ammonia nitrogen is 10% and the amino nitrogen 70% of the total. The tyrosine content is 10% and the cystine 13%. Tryptophane is absent. Values are only approximate. The purified product is rapidly inactivated by trypsin.—F. S. H.

On the preparation and properties of insulin. Somogyi (M.), Doisy (E. A.) & Shaffer (P. A.), J. Biol. Chem. (Balt.), 1924, **59**, xxxiii-xxxiv.

The authors use large amounts of strong acid during extraction to insure the solution of insulin and destruction of proteolytic enzymes. The active material is precipitated by ammonium sulfate and later by adjusting the reaction to pH 5. Details will be reported later.—F. S. H.

Action of insulin on thyroidectomized rabbits (Action de l'insuline sur les lapins éthyroidés). Ducheneau (L.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 248-249.

Thyroidectomized rabbits are more sensitive to the hypoglycemic effect of insulin than control healthy animals. The lowering of the glycemia is more marked and the mortality greater.—T. C. B.

Improvements in the preparation of insulin. Alkaline extraction of the pancreas. Dudley (H. W.) & Starling (W. W.), Biochem. J. (Lond.), 1924, **18**, 147-150.

By a simple modification of the original process of alcoholic extraction of pancreas, namely, by adding sodium bicarbonate to the mixture of minced pancreas and alcohol, the yield of insulin is increased nearly fivefold. An improved technic for the purification of crude insulin by precipitation with picric acid and subsequent conversion of the picrate into soluble hydrochloride is described. At least 90% of the impurities are removed.—F. S. H.

The amount of available insulin in the pancreas of domestic animals. Fenger (F.) & Wilson (R. S.), J. Biol. Chem. (Balt.), 1924, **59**, 83-90.

The authors found that the most important factor in insulin production is absolutely fresh glands. It is also advantageous to break up the cell walls as thoroughly as possible in order to release the insulin and render it available for extraction. The mincing should be followed immediately by a brief but efficient grinding process. The disintegrating processes should be continuous up to the moment the macerated tissue is put into the acidulated alcohol and water mixture in order to minimize the action of trypsin.

Freezing does much harm. The amount of insulin in the pancreas of domestic animals varies from 1,500 to 2,200 rabbit units per kilo of fresh gland. The average yield approximates 1,800 units from cattle, hogs and sheep. The methods employed in separating and standardizing insulin are described in detail. Some of the physical and chemical characteristics of purified insulin are pointed out.—F. S. H.

Presence of toxic and insulin-like substances in oranges, grapefruit and lemons. Fisher (N. F.) & McKinley (E. B.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 248-249.

The authors have separated a hyperglycemia and a hypoglycemia producing substance from the juice, pulp and rind of the fruits examined. The blood sugar reducing substance resembles insulin rather than glucokinin in its physiological action—J. C. D.

The treatment of diabetic coma with insulin. Foster (N. B.), Am. J. M. Sc. (Phila.), 1923, **166**, 699-709.

A detailed report of 15 cases of diabetic coma. Of these 8 recovered, and of the 8 that recovered 5 were still alive at the time of writing. There seemed to be 3 abnormal conditions which are notable in all cases of diabetic coma: acidosis, desiccation of the tissues, and myocardial weakness. While acidosis is primary and in a sense probably initiates other disorders in the body chemistry, it is also true that death may result from one or both of the secondary factors after the acidosis has been corrected. These other factors demand attention in the treatment of diabetic coma. Acidosis is initiated by failure of the oxidation of glucose. The primary object in treatment is to substitute a carbohydrate metabolism for a dominant and progressively imperfect fat metabolism. Insulin makes it possible to accomplish this end, but only when glucose is available for oxidation when the insulin is given. Therefore, it is logical to use glucose in clysters and in beverages.—J. P. S.

New diets in diabetes. Grote (L. R.), Zentralbl. f. innere Med. (Leipz.), 1924, **45**, 3.

Grote reviews the newer methods of dietetic management for diabetes. Fasting is of use in the beginning of the treatment. Petrén's method, using extremely small amounts of proteins (even less than 25 gm.) and very large amounts of fat, gives excellent results. The eventually resulting acidosis is slight and transitory. He believes that the assumption of inevitable ketogenesis from fats is untenable.—J. Am. M. Ass., **82**, 667.

Acetonemia in avitaminosis (Zur Frage der Acetonämie insbesondere bei der Avitaminose). Händel (M.), Biochem. Ztschr. (Berl.), 1924, **144**, 258-264.

Only traces of acetone are to be found in blood of normal persons or animals. The greatest acetonemia was found in dogs 5 or more days after extirpation of the pancreas and in dogs which had been fasted for many days, during which daily injections of phlorizin had been made. A lower degree of acetonemia was found in animals which were simply fasted or treated with the drug. The increase in the acetone bodies in the blood comes largely from beta-oxybutyric acid.—F. S. H.

The respiratory quotients of normal rabbits after the administration of insulin. Hawley (E. E.) & Murlin (J. R.), J. Biol. Chem. (Balt.), 1924, **59**, xxxii-xxxiii.

The respiratory quotient is raised when the blood sugar is lowered by insulin. The object of the experiments was to see whether a purer insulin would produce higher quotients without a depression of the total metabolism, and whether a definite impurity which raises blood sugar (glucagon) would depress the respiratory quotient. The evidence obtained supports the suppositions.—F. S. H.

Old and new treatment of diabetes from a statistical point of view. Heiberg (K. A.), J. Metab. Res. (Morristown), 1923, **3**, 677-678.

The author briefly compares the results of diabetic treatment of diabetes by the old (Allen and Sherrill) method and the new low protein and high fat diet of Petrén. He concludes from the statistics of these various observers that the unmodified method of Allen is superior to that of Petrén.—I. M.

Studies of the effect of exercise in diabetes. I. Change in acid-base equilibrium and their relation to the accumulation of lactic acid and acetone. Himwich (H. E.), Loebel (R. O.) & Barr (P.), J. Biol. Chem. (Balt.), 1924, **59**, 265-293.

These observations were made on man. In the diabetics which were studied there was no evidence that during exercise the body is unable to produce lactic acid or to dispose of it after it is formed. There is no indication that the chemical mechanism of muscular contraction need be anything else than the breakdown of carbohydrate to lactic acid which is utilized in muscular work in normal man. The experiments demonstrate that in the moderately severe diabetic subject short periods of exercise lead to the formation of lactic acid in large amounts and do not cause accumulation of acetone bodies in the circulating blood. From the theoretic point of view the experiments are considered as inconclusive. All the patients were capable of utilizing some carbohydrate. It is considered as quite possible that the subjects studied retained enough of the normal functions of carbohydrate utilization to perform the muscular contractions which were required of them by the usual mechanism and for that reason exhibited the normal accumulation of

lactic acid. A different mechanism might be conceivably employed in completely diabetic patients. In the human subject with complete diabetes exercise sufficient to cause accumulations of lactic acid in the blood is not feasible. Experiments upon lactic acid and acetone production during exercise of completely diabetic animals are in progress. Only hints concerning the effect of exercise upon the well-being of diabetic patients can be obtained from the observations. The two kinds of exercise used were such as might be used by any ambulant diabetic during the course of his daily life routine. No attempt was made to carry the exertion to the point of fatigue. Both types of exercise (short run and longer vigorous walk) seem to produce marked acid production and reduction of alkaline reserve. No alarming depletion of the latter obtained. However, none of the patients had particularly low values at the beginning. The observations do not exclude the possibility of serious damage.—F. S. H.

Studies on carbohydrate metabolism. II. On the preparation of an anti-diabetic hormone from yeast. Part 1. Hutchinson (H. B.), Smith (W.) & Winter (L. B.), Biochem. J. (Lond.), 1923, **17**, 683-692.

It is shown that a substance may be extracted from yeast which has an effect similar to that of **insulin** on the blood sugar of normal animals. When convulsions occur as the result of the injection of this substance, the animals may be restored to normal by injections of glucose. Samples of yeast from different sources yield varying amounts of **glucokynin.** By allowing the yeast to ferment under different conditions, it is found that only in the case of an originally active yeast is the glucokynin formation increased under certain cultural conditions.—F. S. H.

Studies on carbohydrate metabolism. III. On the formation of an anti-diabetic hormone by the action of a bacillus (Preliminary communication). Hutchinson (H. B.), Smith (W.) & Winter (L. B.), Biochem. J. (Lond.), 1923, **17**, 764-767.

A portion of yeast was placed on nutrient agar and a pure culture of a bacillus obtained. Previous tests had shown that an extract of the yeast would cause a slight fall in blood sugar. The bacillus was then cultured and was found to be of the coli form. During the growth of this an insulin-like substance is formed. Injection of the extract into rabbits causes hypoglycemic convulsions which are relieved by glucose.—F. S. H.

Differential diagnosis of diabetes. John (H. J.), Am. J. M. Sc. (Phila.), 1923, **166**, 275-280.

In the diagnosis of diabetes the patient's ability to utilize carbohydrates should be determined. This cannot be determined from an examination of the urine alone. The establishment of the glu-

cose tolerance curve is the only method by which the ability of the individual to utilize carbohydrates can be determined with certainty.
—J. P. S.

A report of sixty-four cases of diabetes mellitus treated with insulin. Jonas (L.), Am. J. M. Sc. (Phila.), 1923, **166**, 687-699.

These cases were divided into three groups: (1) mild cases with no diacetic acid in the urine on admission; (2) cases with reduced CO_2 content of the plasma and with diacetic acid in the urine but with normal plasma pH; and (3) cases with a lowered plasma pH in addition. There were 47 subjects in the first group, 6 in the second and 11 in the third. For treatment these cases were divided into mild and severe, the latter including the second and third groups mentioned above. Five of the 17 patients were in coma when admitted; 6 suffered from acute infections of various kinds. The insulin dosage in the mild cases varied from 5 to 30 units a day; in the severe cases, from 30 to 45 units per day. Of the 5 patients that entered in coma, 2 died within an hour after admission; the other 3 recovered after treatment with insulin. The efficacy of insulin in the control of diabetes during acute infections was striking in all 6 cases; of these, 4 subjects had diabetic gangrene, 1 had carbuncles and 1 lobar pneumonia. The patients treated with insulin showed a drop in blood sugar concentration during the day and a rise at night. The minimum value occurred in the afternoon or early evening and coincided with the time at which hypoglycemic symptoms, characterized by weakness, sweating and headaches, were noted. The amount of insulin sufficient to balance the carbohydrate of a meal might to advantage be given after the meal rather than before it. One of the effects of insulin, particularly in the undernourished, has been gain in weight. This gain is not immediate, however, even on liberal diets.—J. P. S.

The effect of insulin upon the reducing substance in the cerebrospinal fluid of normal rabbits. Kasahara (M.) & Uetani (E.), J. Biol. Chem. (Balt.), 1924, **59**, 433-436.

There is a decrease in the concentration of the reducing substance in the cerebrospinal fluid after subcutaneous administration of insulin. There is some parallelism of the concentration of the reducing substance both in the fluid and blood.—F. S. H.

The effect of insulin upon the complement derived from insulinized guinea pigs for the Wassermann reaction. Kretschmer (O. S.), J. Lab. & Clin. M. (St. Louis), 1924, **9**, 442-443.

It is shown that the pooled serum of guinea pigs made hypoglycemic by treatment with insulin shows no appreciable change in its complementary titer in comparison with pigs not so treated, and retains this property for fully 30 days.—I. B.

The use of fat in diabetes mellitus and the carbohydrate-fat ratio. Ladd (W. S.) & Palmer (W. W.), Am. J. M. Sc. (Phila.), 1923, **166**, 157-169.

The carbohydrate-fat ratio at which the ketone bodies fail to be completely oxidized is apparently fixed, and is the same for both normal and diabetic persons. For practical purposes, the carbohydrate-fat ratio of 1 : 4, calculated from the formula

$$\frac{F}{G} = \frac{\text{Fat in grams}}{0.58 \text{ gm. P.} + \text{gm. CH}}$$

(in which F indicates fat; G, available carbohydrate; P, protein; and CH, carbohydrate) is the most serviceable in the construction of diets where it is desired to obtain a maximum caloric intake with a minimum in the form of carbohydrate. Relatively large amounts of fat may be used in diabetic diets without injury to the patient. There are, however, the following qualifications: (a) The urine can be freed from sugar and acetone bodies more quickly by undernutrition to the point of starvation than by any diet where exogenous fat is substituted for the amount of body-fat assumed to be burned; (b) there is need, as yet, to follow carefully any severe case of diabetes where the ratio is not well within the limits of 1:4; (c) in the presence of infection or an already severe ketonuria, high-fat diets are not advised.—J. P. S.

Action of insulin in Graves' disease (Action de l'insuline sur le syndrome basedowien). Lépine (J.) & Parturier (G.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 269.

All the symptoms of exophthalmic goiter were improved in a man of 48 by injection of insulin for 10 days.—T. C. B.

The influence of insulin on the respiratory exchange and the temperature of the rabbit (Influence de l'insuline sur les échanges respiratoires et la temperature du lapin). Matton (M.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 361-364.

Injection of insulin in rabbits does not alter the CO_2 during the first half hour, after which there is a progressive diminution of CO_2 and of the temperature. At the onset of convulsions there is a temporary augmentation.—T. C. B.

Insulin from fish. McCormick (N. A.) & Noble (E. C.), J. Biol. Chem. (Balt.), 1924, **59**, xxix.

Large islets of insulin-containing tissue occur in the cod and halibut close to the gall-bladder. The insulin obtained from these sources can be used clinically with safety. In several of the species examined it was found that extracts of liver prepared as described contained hyperglycemic producing principles.—F. S. H.

Some favorable effects from the alimentary administration of insulin. Murlin (J. R.), Sutter (C. C.), Allen (R. S.) & Piper (H. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 338-340.

This report gives a table showing the results of duodenal administration of insulin in 2 cases and administration in enteric coated capsules in 2 others. The results are encouraging in both instances.—J. C. D.

Does insulin increase tolerance? Newburgh (L. H.), Boston M. & S. J., 1924, **190**, 352-355.

The author fails to find evidence that insulin increases the sugar tolerance. He supports his conclusions with several case reports.—J. C. D.

Influence of insulin on heat loss in the rabbit (Influence de l'insuline sur la déperdition calorique chez le lapin). Noyons (A. K.), Bouckaert (J.) & Sierens (A.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 365-368.

The first symptom to appear after subcutaneous injection of insulin is a lowering of temperature—even before the depression which precedes the onset of the hypoglycemic crisis. The caloric loss remains that of an animal in repose during the first few hours after the injection. At the end of this period convulsions develop. The curve of heat loss and body temperature descend together and the animal dies in a state of hypothermia. The injection of glucose counteracts these conditions.—T. C. B.

The effect of insulin on the oxygen saturation of hemoglobin. Olmsted (J. M. D.) & Taylor (A. C.), J. Biol. Chem. (Balt.), 1924, **59**, xxx.

A reduction of hemoglobin saturation in the blood is evidently associated with the convulsions caused by insulin hypoglycemia.

—F. S. H.

The value of weight curves in determining the severity of diabetes. Olmsted (W. H.), Med. Clin. N. Am. (Phila.), 1924, **7**, 1631-1644.

Emphasis is laid on the importance of taking a careful history of every diabetic patient, a valuable procedure in determining the probable severity of the case. In diabetics under 35 the disease is usually severe, with rapid reduction in weight. If, however, the young diabetic is of weight normal or above, it is safe to assume that the disease is of mild degree, or that true diabetes does not exist. This is especially true if there has been glycosuria without loss of weight for a period of three or more years. In diabetics past the age of 40 the disease is usually mild, and 75% are overweight. The weight actually lost below the patient's normal standard is the really significant factor to be taken into account.—I. B.

On the normal urine sugar curve in normal individuals, borderline diabetics and severe diabetics under insulin treatment. Page (I. H.), J. Lab. & Clin. M. (St. Louis), 1923, **8**, 631-651.

Observations on the hourly urine sugar curve were made on normal subjects, borderline diabetics, severe diabetics under insulin treatment, renal diabetics, subjects with borderline glycosuria under insulin treatment and with **hyperthyroidism.** The author discusses the use of insulin in borderline glycosuria and describes a standard technic for the determination of the hourly sugar curve. He believes that an examination of the hourly sugar curve will disclose cases of mildly pathological sugar metabolism that would ordinarily be overlooked. This method, on the one hand, detects abnormally high sugar wastage, and, on the other, warns of dangerously low sugar secretion, hence offers an almost ideal method for the control of cases of diabetes under insulin treatment.—I. B.

Action of pancreatic extracts on diabetic animals (Recherches expérimentales sur l'action des extraits pancréatiques dans les phénomènes du diabète chez les animaux). Paulesco, Bull. et mém. Soc. med. d. hôp. de. Par., 1924, **48**, 329-333.

Paulesco claims that successful preparation of effective extract of pancreas was made before the work of Macleod and his collaborators. He refers to his article in Arch. internat. de physiol. for August, 1921. The author was granted patent No. 6254 from the Minister of Industry and Commerce of Roumania for "La Pancréine et le procédé de sa fabrication."—F. S. H.

On the purification of insulin. Piper (H. A.), Allen (R. S.) & Murlin (J. R.), J. Biol. Chem. (Balt.), 1924, **59**, xxxii.

The yield of crude insulin is enormously increased by re-extraction of the precipitates. In spite of all precautions much of the compound is lost in the process of purification.—F. S. H.

The incidence of diabetes mellitus in diseases of the gall bladder and its passages (biometrical study). Rabinowitch (I. M.), Canad. M. Ass. J. (Toronto), 1924, **14**, 296-297.

Analysis of 46,000 hospital cases showed that nine times as many patients with diseases of the gall bladder and its passages (including cholecystitis and cholelithiasis) had diabetes as would be expected if the influencing factors were completely independent.
—A. T. C.

Ketosis and the respiratory exchange in diabetes. Richardson (H. B.) & Ladd (W. S.), J. Biol. Chem. (Balt.), 1924, **58**, 931-968.

The results of these intensive experiments on human subjects indicate that the fatty acid-glucose ratio, calculated from the data

observed with the respiration calorimeter, was parallel with the excretion of the acetone bodies. The threshold of ketosis was found near a ratio of 1.5 to 1.0. This ratio corresponds theoretically to the presence, during oxidation, of 1 molecule of keto-acid for every molecule of glucose. This parallelism is evidence that the respiratory quotient in diabetes is a true measure of oxidation. Diabetic patients were often able to take without undergoing ketosis diets containing a larger proportion of ketogenic substances than is called for by the ratio. This was because the proportions of foodstuffs oxidized were not the same as those ingested. The fall of ketosis observed in diabetic patients as a result of fasting is accounted for by the simultaneous drop in the fatty acid-glucose ratio calculated from the calorimeter data. It was due primarily to a decrease in the total metabolism with a consequent diminution in the metabolism of fats and protein. At the time of fasting there was little or no increase in the total quantity of glucose oxidized when this was computed as being derived from protein and the glycerol of the fat as well as from the carbohydrate undergoing metabolism during the period. Fasting reduces the blood sugar chiefly by depleting the endogenous source of glucose. There is often an increase in the oxidation of glucose during the subsequent period of restricted diet, but this is not necessarily due to the fast.—F. S. H.

The influence of insulin on phlorhizin diabetes. Ringer (M.), J. Biol. Chem. (Balt.), 1923, **58**, 483-501.

Phlorhizinized dogs were treated with insulin. An extensive study of the sugar excretion, the D:N ratio and the basal metabolism was made. From the results it is concluded that insulin injected into completely phlorhizinized dogs results in an oxidation of glucose. A maximum oxidation of 0.95 gm. of glucose per unit of insulin was obtained. Evidence is adduced to show that glucose was also stored as glycogen. Insulin reduced the protein metabolism from its high diabetic level. It caused the disappearance of ketone bodies and reduced the heat production by 2 calories per hour. The bearing of these data on the mechanism of phlorhizin diabetes is discussed. The argument is brought forth that the striking effect of insulin in correcting diabetes of a phlorhizinized dog indicates that phlorhizin transitorily injures the pancreas by preventing the production of the antidiabetic hormone. The use of phlorhizinized dogs in the assay of insulin is proposed.—F. S. H.

The treatment of diabetes with insulin. A report of the methods followed and the results obtained in the first one hundred cases. Sansum (W. D.), Blatherwick (N. R.), Smith (F. H.), Long (M. L.), Maxwell (L. C.), Hill (E.), McCarty (R.), & Cryst (J. H.), J. Metab. Res. (Morristown), 1923, **3**, 641-676.

Part of the insulin used was obtained from the Eli Lilly Co.,

but about five-sixths of the quantity used was made by the authors themselves according to the method of Collip. The objects of treatment constantly before them were: (1) that the patient should be kept continuously "sugar free," and that the blood sugar should be normal; (2) that the patient should be kept continuously free from acidosis; and (3) that the patient should be nourished as evidenced by a satisfactory weight. When diet alone was inadequate for the accomplishment of these aims insulin was used also. Four conditions should be fulfilled, according to the authors, in the treatment of diabetes with insulin: (1) the sugar utilizing power of the insulin in grams per cubic centimeter should be known; (2) the patient's natural tolerance should be determined in grams of sugar formers; (3) the exact diet should be known; and (4) the dosage of insulin may then be adjusted to make up the difference between the sugar formers of the proposed diet and those of the patient's natural tolerance. The symptoms and treatment of insulin overdosage, the necessity for education of the patient and a detailed outline of diets used are discussed. The results of insulin treatment obtained are confirmatory of the results of others working in this field. Patients with insulin plus diet therapy developed an increase in tolerance more quickly than those on diet alone.—I. M.

Some chemical reactions of the substance containing insulin. Shonle (H. A.) & Waldo (J. H.), J. Biol. Chem. (Balt.), 1924, **58**, 731-736.

From the discursive data given in this paper it is concluded that the pancreatic substance containing insulin appears to be a complex mixture of proteoses, which give typical protein reactions and from which it has as yet been impossible to isolate a simple substance or to detect a chemical reaction that is characteristic of the physiologically active constituent.—F. S. H.

The duration and magnitude of the hypoglycemia after insulin. Severinghaus (E. L.), Kirk (Elizabeth) & Heath (H. J.), Am. J. M. Sc. (Phila.), 1923, **166**, 677-686.

Eight students who had not had breakfast on the morning of the tests were divided into three groups and given 4, 8 and 10 units of insulin, respectively. Blood sugar was estimated by the method of Folin and Wu. Another group of students who had not had breakfast on the morning of the experiment was given 100 grams of glucose dissolved in 200 cc. of water to which had been added the juice of one lemon. Their sugar tolerance was investigated, the sugar content of the urine being determined by the method of Folin and Berglund. Two or three days later the same students were submitted to the same test except that immediately after the sugar solution had been swallowed, each was given an injection of insulin varying from 8 to 16 units. From their experiments the authors

conclude that in normal human subjects the extent and the duration of the hypoglycemia after the injection of insulin are so variable that the result cannot be predicted from the dose per kilo of body weight. The extent of the hypoglycemia and the duration of the low level are roughly parallel to the dose of insulin. The depression of the sugar tolerance curves by insulin is not uniform in type or extent. With increasing dosage of insulin both the extent and the duration of the hypoglycemia are increased. The blood sugar concentration at which symptoms of overdosage of insulin appear varies in different individuals in the region of from 40 mg. to 65 mg. per 100 cc. of blood. The concentration of sugar in the urines of normal subjects does not follow the blood sugar level with or without insulin. It is related more closely to the urine volume. The treatment of diabetics with small doses of insulin at intervals of not less than 6 hours is preferred to the use of larger doses at very long intervals, or of smaller doses at too short intervals. Intranasal application of insulin is without effect.—J. P. S.

Some attempts to administer insulin per rectum (Quelques essais d'administration de l'insuline par le rectum). Stenström (T.), Compt. rend. Soc. de biol. (Par.), 1924, **90**, 518-520.

In mice ten times the lethal dose of insulin, given by rectum, is without effect, due to the destructive action of the ferments of the intestinal contents on insulin.—T. C. B.

On the blood phosphates after insulin convulsions. Winter (L. B.) & Smith (W.), J. Physiol. (Lond.), 1924, **58**, 327-333.

Rabbits have been successfully treated in insulin convulsions by **adrenalin, pituitary** extract and glucose. After adrenalin the inorganic phosphate usually regains the normal level quickly and falls again. With pituitrin the effect is variable. After glucose the normal volume is not regained for some time.—T. C. B.

The action of ammonium hydroxide and other alkaline compounds upon insulin. Witzemann (E. J.) & Livshis (L.), J. Biol. Chem. (Balt.), 1923, **58**, 463-474.

The results described in this paper show that insulin is more or less completely inactivated at room temperature by 0.5 or 0.7 N ammonium hydroxide in the course of some days, and that its original activity is usually quickly restored on acidification with hydrochloric acid. It was also found that sodium and potassium hydroxides even at 0.1 N concentration irreversibly inactivate insulin at room temperature. Sodium carbonate and bicarbonate and disodium phosphate had almost no effect. Some exploratory experiments on the effects of mixed alkalies indicated that the above reactions are also subject to secondary accelerative and retarding effects, depend-

ing upon the mixture used. They suggest a tautomeric rearrangement.—F. S. H.

Some milder forms of diabetes with special reference to mild diabetes in elderly persons with arteriosclerosis. Woodyatt (R. L.), South. M. J. (Birmingham), 1924, **17**, 145-153.

The author calls attention to a type of case in which the patient shows some sugar in the urine over a long period, but no thirst and no loss of weight. He is able to burn most of the sugar taken in, even though that amount be large, but is not able to burn it all even when the intake is reduced to a very low point. **Insulin** has little influence in such cases. Care should be taken not to cripple such patients by reducing the diet when the sugar leakage is not a dangerous symptom. Dietary methods for testing this with case histories and charts are included in the article.—J. C. D.

Parathyroids in anthropoid apes (Epithelkörperchenbefunde bei Menschenaffen). Arndt (H. J.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1923, **68**, 514-522.

Gross and microscopical description of the parathyroids in 3 chimpanzees. Some literature is cited.—A. T. R.

Experiments with an active extract of parathyroid. Ellingson (E. O.), Bell (A. W.) & Hanson (A. M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 274-275.

By boiling finely divided ox parathyroids with dilute HCl the authors obtained an extract which they think contains the active principle of the parathyroid. After its administration dogs showing convulsions recovered and it has been beneficial in gastric, duodenal, and varicose ulcers and several other types of chronic inflammation. Its effects resemble those following a relative increase of the ionic calcium in the blood. The active principle itself has not been isolated.—J. C. D.

Are guanidines present in the urines of parathyroidectomized dogs? Greenwald (I.), J. Biol. Chem. (Balt.), 1924, **59**, 329-337.

By using a carefully controlled and new method of chemical analysis Greenwald was unable to demonstrate the presence of more than 0.5% of guanidine nitrogen (in terms of total nitrogen) in the urine of parathyroidectomized dogs. From the fact that a high percentage of recovery of added guanidine to the urine was attainable by the new method and other arguments given in the body of the paper, it is evident that but little justification is to be had for considering that parathyroid tetany is due to guanidine intoxication until further evidence is available. No theory of the causation of tetany can be considered adequate if it fails to take into account

the changes in calcium and phosphorus in the blood and urine as being intimately connected with the sequence of symptoms observed.
—F. S. H.

Treatment of chronic postoperative tetany by intravenous injections of calcium chloride and injections of parathyroid extract in large doses (Le traitement de la tétanie chronique post-opératoire par les injections intraveineuses de chlorure de calcium et les injections d'extrait parathyroidien à hautes doses). Sainton (P.), Bull. et mém. Soc. méd. d. hôp. de Par., 1923, **47**, 1576-1578.

The case is reported of a woman of 35 with a large goiter. This was removed and 3 days later tetany set in, appearing at 8-day intervals. Although the attack could be alleviated by ingestion of calcium chloride, the situation continued for four years with increasing involvements. Intravenous injection of 1 gram of the calcium compound in 3 cc. was then attempted with brilliant success, insofar as aborting impending attacks. The solution was diluted from 3 to 10 cc., however. Later on specially prepared extracts of the parathyroid glands were administered intravenously, beginning with a dose equivalent to 0.05 gram and gradually raising it to 0.15 gram. The attacks disappeared completely following this intensive medication.—F. S. H.

Studies on the physiology of the parathyroids. Salvesen (H. A.), Acta med. Scand. (Stockholm), 1923, Suppl. **6**, 5-159.

Salvesen carried out an elaborate metabolic study on 7 dogs with partial and 10 with complete parathyroidectomy. He concluded that the drop in blood calcium caused by parathyroidectomy is not due to anesthetics or acidosis. Parathyroidectomy causes no hypoglycemia. The observation that the alkali reserve decreases and the acid excretion increases indicates that there exists no alkalosis after parathyroidectomy. The characteristic feature in the chemistry of parathyroid insufficiency is the drop in blood calcium. The beneficial action of calcium injections on the symptoms of tetanic dogs is so short because the calcium disappears rapidly from the blood. Completely parathyroidectomized dogs can be preserved by calcium treatment and pass into a state of latent tetany. Latent tetany is characterized by a low blood calcium. It is the withdrawal of milk which is responsible for the dietary production of tetany in latent tetanic dogs. Milk prevents tetany by its calcium content. The cause of the lowered glucose tolerance in parathyroidectomized dogs is the decrease in blood calcium. There is a relation between sugar metabolism and the calcium-phosphorus metabolism. Guanidin acts as a convulsive poison without altering the calcium or phosphates of the blood. All the symptoms of parathyroid insufficiency are due to calcium deficiency, which is indicated by the drop in serum calcium. Calcium deficiency causes dysfunction of probably all organs. The

calcium deficiency is due to increased excretion of calcium through the intestines. The cause of this "lowered threshold" is not known. It is not caused by guanidin poisoning. The parathyroids control the calcium level of the blood and by doing so they influence the function not only of the muscle and nerve tissue, but probably of all organs and all cells. How this control is exerted is not known. Life is under certain conditions (calcium administration) possible without the parathyroids. Infantile tetany is probably due to an existing parathyroid insufficiency. Epilepsy, eclampsia and paralysis agitans are not due to parathyroid insufficiency. A good working bibliography and review of the literature are included.—R. G. H.

The relation between calcium and protein of serum in tetany due to parathyroidectomy. Salvesen (H. A.) & Linder (G. C.), J. Biol. Chem. (Balt.), 1923, **58**, 635-639.

It was found that the plasma protein content of the blood is not affected by parathyroid removal and the consequent tetany in dogs. The calcium content dropped. This is taken as an indication that the calcium decrease in tetany is not due to a primary decrease in the protein bound calcium, but is caused by a decrease in the diffusible fraction.—F. S. H.

A contribution to the study of the pineal body. Izawa (Y.), Am. J. M. Sc. (Phila.), 1923, **166**, 184-196.

A report of a study of 4 pinealectomized chickens (3 males and 1 female). Izawa concludes that pinealectomized young cocks grow more rapidly than the controls, begin to crow prematurely, and show an earlier development of comb and testes. Pinealectomized young hens likewise reveal a premature development of ovary and Fallopian tube. In pinealectomized chickens the endocrine organs, except for the sex glands, show nothing abnormal, or only slight differences, as compared with those of the controls. It appears, therefore, that the pineal body's chief function is to repress the premature development of the sex organs in the female as well as in the male. The details of the results upon which the above conclusions are drawn are tabulated, and from this table the following facts may be cited: one pinealectomized cock 210 days old, weighed 1820 grams, its testes weighed 14.3 grams, and the relative weight of testes in grams to a kilogram of body weight was 7.85; the control of the same age weighed 1200 grams, its testes weighed 1.49 grams, and the relative weight of testes in grams to a kilogram of body weight was 1.24. The corresponding weights in a second pinealectomized cock 251 days old were 1950 grams, 18 grams, and 9.7, respectively; while the control of the same age showed corresponding weights: 1600 grams, 7.0 grams, and 4.3, respectively. The body weight of the pinealectomized hen was about 40% greater and

that of the ovaries slightly more than 100% greater than the corresponding weights in the control hen of the same age.—J. P. S.

Pineal gland secretion in man and some animals (Contributo allo studio della glandola pineale nell'uomo e in alcuni animali). Clemente (G.), Endocrin. e patol. costituz. (Roma), 1923, **1**, 44-47; abst., Ber. ü. d. ges. Physiol. (Berl.), 1924, **23**, 447.

In chronic diseases, especially those which influence circulation, the pineal gland undergoes regressive variations which accompany similar changes in the **hypophysis**. In animals (rabbits, porpoises) in which the pineal had been removed pregnancy nevertheless occurred. Young animals in which the thyroid gland had been removed showed premature development of the secondary sexual characteristics and of the **testes**.—M. D. G.

Further observations upon the shadows of the thymus and the heart. De Buys (L. R.) & Samuels (E. C.), South. M. J. (Birmingham), 1924, **17**, 260-264.

The observations were carried out in the first year of life. The points of endocrine interest are that the thymus and heart shadows are independent in size and position and that the thymus shadows may undergo changes in size without any visible symptoms in the patient.—J. C. D.

The respiratory exchange of rats without spleens (Beiträge zur Physiologie der Drüsen. 60. L. Asher. Erneute Untersuchung über den respiratorischer Grundumsatz normaler und milzloser Ratten). Takahashi (Y.), Biochem. Ztschr. (Berl.), 1924, **145**, 130-153.

These studies indicate that splenectomy lowers the respiratory exchange. The presence or absence of iron in the food has no perceptible effect. The nitrogen excretion of the rats was increased by splenectomy in the majority of cases. Splenectomized rats respond more strongly to **thyroid** feeding than normal animals.—F. S. H.

The effects of extirpation of the thymus (Sugli effetti della timectomia). Pighini (G.), Biochem. e terap. sper. (Modena), 1922, **9**, 207-219.

Before puberty the thymus is indispensable to the nuclein lipoid and calcium metabolism. This is demonstrated by surgical extirpation, vagotomy, x-rays or radium, adrenalin intoxication, or a diet deprived of vitamin B.—P. M. N.

An epidemic of acute goiter in a children's home. Adams (E. W.) & Crossley (H. N.), Lancet (Lond.), 1923, **ii**, 500.

A description is given of a small outbreak of acute goiter occurring in one cottage out of a colony of 9 constituting a Children's

Cottage Home. The homes were situated near the village of Wardle. The authors state that the chronic form of goiter seems to be rife among the children of all the cottages, but the acute epidemic was limited to one. There were 8 occupants, boys between the ages of 4 and 10 years, and all were affected. The adult staff escaped. There was no complete record of the previous thyroid state, but one of them was known to have a somewhat enlarged thyroid. On January 10 the boy who had previously had a slight swelling of the thyroid developed a very marked enlargement. On the 12th a similar enlargement was noticed in 2 other boys, and on the 13th the remaining 5 were affected. The right lobe was invariably more affected than the left, and there were no glandular enlargements. The swelling was soft, elastic, painless and non-inflammatory, and in some there were carotid thrills and enlarged venules. The temperature was normal and remained so, and the general health was unimpaired. The bacteriological reports on the throats were negative as regards diphtheria, but gave the predominating organisms as streptococci. After a period varying from 5 to 7 days the thyroids began to subside. The subsidence continued for about a fortnight and then passed into a stationary period. By February 1, one of the cases had returned to normal. On March 6, 3 of the thyroids would not have attracted attention, while in 4 of the others it was only slight. In only one did the enlargement remain considerable. On May 22, 5 of the thyroids were normal, 2 were very slight, and in 1—the boy in whom the condition had started—there was still an appreciable enlargement. No definite etiological factor could be determined at the cottage. The only infection had been a slight epidemic of measles which had cleared up a month before. Goiter is endemic in the district and is not uncommon among the children. In the cottage population of 83 children there were 33 cases of chronic thyroid enlargement as compared with 30 cases among the 249 school children in the neighborhood, thus showing that there was a greater tendency for the chronic variety in these cottages. No differences were determined between the conditions of life in this cottage and those of the other cottages.—Med. Sc., **10**, 57.

Modifications of lipoid content of the liver after thyroidectomy (Sulle modificazioni del contenuto in liqoidi del fegato dopo la tiroidectomia). Artom (C.), Arch. di sc. biol. (Napoli), 1923, **5**, 22-43.

It is concluded from a study of their experiments that thyroid deficiency causes modifications of fatty acids and fat metabolism.
—P. M. N.

Effect of polar ligations upon the remaining lobe of thyroid gland after removal of one lobe. Barber (W. H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 239-240.

This is based on a study of 32 dogs. Very few of the glands

involved remained normal after the operation. Degenerative changes were found likewise in two-thirds of the **parathyroids** seen.
—J. C. D.

Exophthalmic goiter. Barker (L. F.), Internat. Clin. (Phila.), 1924, **1**, s. 34, 1-16.

This is a clinical lecture on exophthalmic goiter detailing the history and treatment of an exemplifying case. The diagnosis of the disease is easily made in the presence of more than two cardinal symptoms. Toxic adenoma may resemble Graves' syndrome; in the former condition the shelling out of the adenoma by the surgeon results in clear-cut recovery, while treatment of exophthalmic goiter is not quite so precise. Treatment frequently results in subsidence of symptoms, but recurrence is common, and though many are restored to ordinary health and to economic productivity, all require most careful medical supervision throughout life. Exophthalmic goiter is a pluriglandular endocrinopathy, with involvement also of the vegetative nervous system and often of the higher cerebral centers. Barker believes that these individuals possess a basic predisposition to the disease, superimposed upon which psychic trauma, focal infection and other known and unknown factors may serve as exciting causes, bringing to the surface the entire symptom-complex. Surgical treatment, though associated with a much lowered operative mortality rate than heretofore, still carries with it the danger of such post-operative events as acute hypothyroidism, accidents of anesthesia, etc. In medical as well as in surgical treatment, physical and mental rest are of primary importance and should be instituted early. Diet, hydrotherapy, drugs, psychotherapy, and roentgenotherapy play their parts. The fattening of the subject under treatment seems desirable.—I. B.

Auricular fibrillation in goiter. Baumgartner (E. A.), Webb (C. W.) & Schoonmaker (H.), Arch. Int. Med. (Chicago), 1924, **33**, 500-512.

The authors report 3 cases and review the literature. In summary they say: "Germain Sée, in 1878, described irregular, rapid pulse and heart in cases of goiter in which there was probably fibrillation. Twenty cases, besides a series of 18 by Hamilton and figures from other clinics, have been reviewed. Fibrillation may occur in hyperthyroidism, in both adenoma and exophthalmic cases, and may be paroxysmal or permanent for months or years. These patients should be given digitalis as other patients with fibrillation are given it, and operation should be performed even if there is fibrillation. We believe, as was stated in Schoonmaker and Webb's report, that the 'gravity of the heart condition relative to thyroidectomy has been repeatedly overestimated, resulting in delay in operation and in a borderline dangerous myocardial insufficiency.'"
—R. G. H.

The roentgen rays in thyroid therapy. Bierman (M. I.), Minnesota Med. (St. Paul), 1923, **6**, 322.

The effects of radiation upon thyroid tumors as well as upon other neoplastic tissue formations are primarily direct, acting on the cells themselves. The rays affect the protoplasm as well as the nucleus of the cell, but the interference with the nucleus is usually of much greater significance for the function of the cell than the localized changes in the cytoplasm, as any marked interference with the nucleus results in the death of the cell. The changes produced in the cells are attended by no risk whatever to the patient provided that the ordinary precautions peculiar to x-ray treatment are observed. It is true that the surgical removal of the thyroid will produce results much more rapidly than roentgen ray treatment; but the uncertainty of improvement, the dangers of operation, and the advisability of first using less extreme measures of treatment will militate against operative interference in favor of radiation. Radiation is the treatment of choice in all types of toxic goiter. The author uses an 8 or 9-inch spark gap; 3 to 6 mm. aluminum filter; cross-fire method; repeated at intervals of 2 to 3 weeks. It is not advisable to produce even a mild erythema and it is important to maintain a check on the effects of radiation by observations of the metabolic rate. When this decreases rapidly to 25 or 30% below normal it is well to discontinue treatment. The changes produced by x-ray continue to exert their influence for as long as two to three months after the last treatment and if treatment were continued until the metabolic rate reached normal the final result would be a negative rate or hypothyroidism. The treatment of thyroids by roentgen ray is necessarily a long drawn out procedure extending over many months and at times even requiring two or three years for a complete cure, and the treatment is rather of benefit only in selected cases which show undoubted metabolic hyperactivity. The adenomatous and exophthalmic types are especially favorable. Other forms such as simple goiter, colloid goiter, the cystic goiter, and the goiter of adolescence are not proper subjects for roentgen ray treatment.—Radiology, **1**, 127.

Disturbances in Metabolism. I. Variations in protein metabolism as indicated by sulfur excretion. Goiter. Craig (J. Mc.) & Harington (C. R.), Biochem. J. (Lond.), 1924, **18**, 85-92.

It is concluded that the increase in metabolism in exophthalmic goiter is due primarily to the acceleration of the endogenous oxidative processes, the increase in tissue breakdown being secondary to this effect. The results in **myxedema** are difficult of explanation. The theory developed from the observations leads to the idea that a low-protein diet is contra-indicated in hyperthyroidism. Acting on this assumption it was found that the basal metabolism tends to be lower on a rich protein diet and no ill effects obtained.—F. S. H.

Ovarian opotherapy and goiter (Opothérapie ovarienne et goitre). Coulaud (E.), Ann. de méd. (Par.), 1923, **14**, 517-534.

After reviewing briefly the literature concerned with the relation of the thyroid to the sexual cycle in women, the author reports a large series of cases in which goiter was treated by ingestion of ovarian products (dose from 0.2 to 0.4 gr. per day for 3 months). In 6 patients the results were negative; in 9 the circumference of the neck was not diminished but softening of the goiter occurred; in 59 the circumference of the neck was diminished from 1 to 3 centimeters; in 17 the diminution ranged from 3.5 to 7; and in 9 subjects the goiter disappeared. No other medication was employed. In the post-climacteric goitrous cases ovarian treatment was followed by loss of weight in those who showed a tendency toward adiposity. In those who had not reached the menopause the effect was not produced. It is therefore concluded that ovarian opotherapy is efficacious in the treatment of goiter and has no contra-indications. Administration of ovarian products over a long period of time produced no modification of the incretory glands of the rabbit.—F. S. H.

The influence of thyroid substance on the absorption of pleural effusions. Danzer (C. S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 298-301.

Three subjects with parapneumonic pleural effusion were treated with thyroid substances. The effusion was more rapidly absorbed than is usual. No results followed in a case of primary pleural effusion, probably tubercular.—J. C. D.

The relationship of goiter to mental disorders. Foss (H. L.) & Jackson (J. A.), Am. J. M. Sc. (Phila.), 1924, **167**, 724-735.

The close observation of about 800 goiter cases coming to a general hospital for treatment and the simultaneous study of 50 goiter patients among 1700 inmates of a large hospital for the insane, both institutions in the same locality and drawing their patients from the same territory, led Foss and Jackson to conclude that goiter is not, even in a goitrous district, especially common in the insane; rather the reverse, for its incidence in the State Hospital at Danville, Pa., is but 3%. Conversely, insanity is extremely rare among the large number of goiter patients applying for treatment in a general hospital in the same locality, there being no cases of true insanity among the 800 patients studied, the only mental disturbance being in the form of a mild excitement or rarely slight and transient mania, this in but 2 cases. There is, apparently, no definite relationship between goiter and insanity and surely nothing to indicate thyroidectomy in the treatment of the usual insane patient suffering from complicating goiter, unless for the relief of mechanical pressure. Operation, of course, may be indicated if there be accom-

panying evidences of true hyperthyroidism, but this latter condition is most rare. Neither hyperthyroidism nor hypothyroidism occurs, except very rarely, among the adult goiter patients of the Pennsylvania hospitals for the insane, the greatest number of goiters being of the so-called multiple adenomatous or nodular forms and unaccompanied by systemic disturbances.—R. G. H.

Thyroid physiology in the frog (Contributo allo studio della fisiologia della tiroide della rana). Gayda (T.), Gior. d. r. Accad. di med. (Torino), 1921, **4 s. 27,** 405-407.

In the frog the thyroid seems to be important only when the organism is developing. In the adult thyroid extirpation or enteral or parenteral thyroid administration gives no notable results.
—P. M. N.

Basal metabolism in office practice. Haller (D. A.) & Clayton (M. M.), J. Lab. & Clin. M. (St. Louis), 1924, **9,** 437-443.

This is a report of a series of observations to substantiate the opinion that basal metabolic determinations can be successfully made in the physician's office.—I. B.

The effect of thyroid and parathyroid deficiency on the gross chemical composition of the long bones. Hammett (F. S.), J. Biol. Chem. (Balt.), 1924, **59,** xli.

When the thyroid apparatus is removed from albino rats 100 days of age a distortion of the course of differential development in gross chemical composition is exhibited. The nature of the disturbance consists of a combined partial desiccation and a retardation of ossification. When the parathyroids alone are removed there is no such change in the male; but in the female retardation of ossification is evident.—Author's Abst.

The differential diagnosis between beginning or low-grade hyperthyroidism and the exhaustion of the body due to focal infections. Hoxie (G. W.), Med. Clin. N. Am. (Phila.), 1924, **7,** 1119-1126.

This is a report of 4 cases in which, because of the vague clinical pictures, the diagnosis was at first uncertain. Calorimetric tests are of great value in these borderline cases. Exhaustion of the resistance of the body such as may occur in the presence of focal infections may give rise to diminished sugar tolerance; this must not be hastily attributed to a primary endocrine disturbance.—I. B.

The differential blood count in hypothyroidism. Hutton (J. H.), Illinois M. J. (Oak Park), 1924, **45,** 272-273.

Hutton believes that thyroid hyposecretion is associated with a reduction in the percentage of polynuclear leucocytes. In a study

of 29 cases presenting a basal metabolic rate of from minus 6 to minus 28%, the polynuclear count averaged 60%. The author concludes that there is a probable relationship between the percentage of polynuclears and the state of activity of the thyroid gland, and that this is related to the problems of immunity of the body to infections.—I. B.

Exophthalmic goiter and involuntary nervous system. Hyman (H. T.) & Kessel (L.), Arch. Surg. (Chicago), 1924, **8**, 149-165.

The course of subjective and objective manifestations in 50 unselected patients observed by Hyman and Kessel over a period of 2 years, in whom no specific therapeutic measures were instituted, is detailed. Apparently the spontaneous course of exophthalmic goiter is toward economic restitution in the majority of cases (83%). Recovery was not complete in the sense of cure, but was marked by the persistence of residual subjective symptoms. These residual symptoms did not interfere with economic restitution. In at least the first two years of remissions, severe incapacitating exacerbations were infrequent. These results of "skillful neglect" compare favorably with the results of specific therapeutic measures.—J. Am. M. Ass., **82**, 822.

Hyperthyroidism complicating pregnancy. Jackson (A. S.), Ann. Clin. Med. (Balt.), 1924, **2**, 303-311.

The occurrence of hyperthyroidism in pregnancy is increasing, due to the spread of goiter. The literature indicates that in the past a very conservative view has been maintained with regard to thyroidectomy in cases of goiter associated with pregnancy. The early diagnosis of toxic goiter (due largely to the recognition of the value of the basal metabolic rate), the perfection of teamwork in the operating room, and the discovery of the newer methods of treatment have been the means of reducing the operative mortality to a minimum. These advances should influence the obstetrician not to delay surgical intervention in the thyroid either in exophthalmic goiter or in frank cases of toxic adenoma. The necessity for therapeutic abortion is now of rare occurrence. Medical treatment is indicated only in mild cases of toxic adenoma or in incipient cases of exophthalmic goiter developing near the termination of pregnancy. Thyroidectomy in the two cases reported here proved as safe as in cases not associated with pregnancy.—Quoted from Original.

Endemic goiter. Keith (W. D.), Canad. M. Ass. J. (Toronto), 1924, **14**, 284-289.

This paper is a valuable study of goiter in the Pemberton Valley, B. C. (45 to 50 miles long, in the Coast Range, watered by the Lilloet River, fed directly from a glacier), based largely on the observations of John Ronayne, a large farmer in the valley, supple-

mented and confirmed with histological examination of different thyroid material. At the end of 1917 many men, almost every woman, and every child born in the valley had goiter. Large litters of pigs were born, most of which were hairless and died within a day. Those with some hair which survived a few days became hopelessly myxedematous. In these the thyroid was larger than usual, dark red, and engorged with blood. All cows had some slight enlargement of the thyroid and gave birth to goitrous calves, of which few survived, and some of these were cretins. Many cows producing goitrous calves carried them a month over usual term. All mares became goitrous, and after being in the district 3 years their foals were goitrous. The second colts were carried 12 and sometimes 13 months, and were goitrous; few survived. These, 15% were carried only 11 to 11.5 months. The meconium in the colts that died was rubbery in consistency. The farm animals were more subject to goiter or exhibited it more in late winter and early spring. Chickens, ducks and turkeys brought into the valley appeared to thrive, but their eggs, though producing embryos, failed to hatch out, the apparent cause being thickening of the white envelope within the shell (which became rubbery). Marine's procedure of iodide administration was applied to animals and birds. In October, 1922, no goiter could be found in the valley. No wild animals killed in the district showed an enlarged thyroid. The district is virgin soil with a remarkably pure water supply. The disease was more pronounced higher up the valley. Poor sanitation existed only in the Indian village at the lower end of the valley; here no goiter occurred in human beings or pigs. Endemic goiter found under such conditions appears to be an iodine-deficiency disease. Iodine is now given only in winter and early spring. Some results were obtained suggesting that excess of iodine caused a lack of fecundity.

—A. T. C.

The chemical reactions involved in the physiological functioning of thyroxin. Kendall (E. C.), J. Biol. Chem. (Balt.), 1924, **59**, xxxix.

During the synthetic work leading to the elaboration of thyroxin a derivative was produced which differed from thyroxin in having one more bond and two less hydrogens. Both of these forms occur in the thyroid gland. The function of the thyroxin is to regulate the capacity of the cell to use oxygen. The rate of this functioning depends on the physical state of the cell. The alternate oxidation and reduction is regulated by the opening and closing of the pyrrol ring in the tissues. This is in turn dependent upon the concentration of positive and negative charges present. It therefore appears that thyroxin makes any cell more sensitive to external—that is, physical—conditions.—F. S. H.

Toxic substances in the serum of thyroidless and parathyroidless animals studied by means of the respiratory exchange (Beiträge zur Physiologie der Drüsen. 58. Leon Asher. Prüfung der Frage von giftigen Stoffen im Serum schilddrüsenloser und parathyreopriver Tiere mit Hilfe des respiratorischen Grundumsatzes). Jino (K.), Biochem. Ztschr. (Berl.), 1924, **145**, 105-115.

Rabbit serum when injected intraperitoneally into rats in amounts from 1 to 2 cc. raises the respiratory exchange slightly. The serum of completely thyroidectomized rabbits does the same, though to a lesser degree. This fact is evidence against the assumption of the presence of toxic substances in the blood sera of thyroidless animals. When serum from rabbits at the height of parathyroid tetany is injected into rats there is produced a marked lowering of the respiratory exchange.—F. S. H.

A review of another year's work with thyroid disease. Lahey (F. H.), Boston M. & S. J., 1924, **190**, 153-157.

The author concludes that thyroid extract is contraindicated in toxic cases and that prolonged iodine feeding may convert non-toxic into toxic goiter. Hyperthyroidism does not exist in the absence of increased basal metabolism rate and cures of hyperthyroidism are not accomplished without returns of basal metabolism rate to normal, provided there are no conditions other than a thyroidism elevating it. Basal metabolism readings are of great value in neuroses simulating thyroidism, in that the true basal metabolism rate in the neurosis is normal. Basal metabolism readings uncorrelated are not a reliable guide to the number or extent of operations a patient will stand. Minus degrees of basal metabolism rate may exist in patients free from clinical evidence of myxedema, yet made subjectively better by raising the rate to normal with thyroid feeding. Multiple stage measures are life-saving procedures in severe hyperthyroidism. Thyro-cardiac cases first seen in decompensation may be restored to striking cardiac capacity if it is possible by thyroidectomy to remove the intoxication and to restore the heart rate to within normal limits. The most dreaded, uncertain and uncontrollable factor in the author's clinic today is mediastinitis. The moderate values of x-ray treatment are more than outweighed by its disadvantages. Thyroid surgery done in a general surgical clinic equipped for the care and study of these subjects will show few failures to cure and a mortality rate rarely over and in most cases under 1%.—J. C. D.

Basal metabolic rates in some of the psychoneuroses. Levine (B. S.), J. Lab. & Clin. M. (St. Louis), 1923, **8**, 775-789.

This report is based upon basal metabolic determinations carried out in 100 cases presenting two or more cardinal signs of hyperthyroidism. The primary complaint in all patients was nervousness.

The author reviews the recent literature bearing on the relationship between nervous conditions, thyroid disorders and abnormal metabolic rate, and finds that in the main there is but little consistency of opinion. Of the 100 cases studied, 15% presented a rate in excess of plus 10, and 4% presented a rate below minus 10. The average of the plus rates of the entire series was plus 7.4%, and that of the minus rates minus 6.5%, the total average rate being plus 2.0%. Of the cases with rates exceeding plus 10%, 15% were classified as hysterics, 24% as neurasthenics, and 12.5% as possessing one of the anxieties. Of the cases with metabolic rates below minus 10%, 7% were classified as hysterics, 4% as neurasthenics, with no anxieties. The author believes that in the case of the "high rate" psychoneurotics, hyperthyroidism or exophthalmic goiter was superimposed as a sequel and is a direct consequence of the mental status. Surgical treatment of the thyroid is therefore an erroneous procedure and means the introduction into the patient's life of new points of fixation, added emotionalism with an increased demand upon the thyroid and a higher basal metabolic rate than existed before the operation.—I. B.

Hyperthyroidism masked as heart disease. Levine (S. A.) & Sturgis (C. C.), Boston M. & S. J., 1924, **190**, 233-237.

Five cases are reported and discussed. In each case the usual signs of Graves' disease were absent. Attacks of auricular fibrillation suggested hyperthyroidism and this diagnosis was confirmed by the subsequent history.—J. C. D.

Influenza and hyperthyroidism. Marañón (G.), Arch. de endocrin. y nutric. (Madrid), 1924, **1**, 1-16.

Marañón states that he has encountered 18 cases in which pronounced hyperthyroidism developed in connection with an attack of influenza. This group forms 2.7% of his 657 cases of hyperthyroidism during the past 5 years. He has very rarely observed hyperthyroidism following any other acute infectious disease, and in his 1300 cases of excessive functioning of the thyroid he always was answered in the negative when inquiring as to acute febrile rheumatism in the past. In his post-influenzal hyperthyroidism cases there were seldom any clinical indications of thyroiditis, but in nearly every case the thyroid was chronically enlarged.—J. Am. M. Ass., **82**, 1403.

The use of Lugol's solution in the treatment of exophthalmic goiter. Mason (E. H.), Canad. M. Ass. J. (Toronto), 1924, **14**, 219-221.

Details of 5 cases are given, showing the great rapidity with which Lugol's solution (iodine 5%, potassium iodide 10%) lowers the pulse rate and basal metabolism to normal in true exophthalmic goiter, after which normal conditions can be maintained with small

doses. If there is total cessation of this treatment the toxic condition may return quickly. The maximum dose employed was 0.118 gram iodine per day. The author considers that such results favor the view that Graves' disease is due to an abnormally formed chemical complex, possibly an imperfectly iodized thyroxin molecule.

—A. T. C.

Significance of the thyroid in the production of immune bodies. Misawa (T.), Fukuoka Ikadaigaku Zasshi (Fukuoka), 1923, **16**, 174-194.

The rate of the production of immune-hemolysin, precipitin, and hemolysing complement was observed on rabbits with the thyroid removed or fed with the thyroid preparation. No change in the production attributable to these procedures was found.—K. H.

The Kottmann reaction for thyroid activity. Carbon dioxide in the tested serum. Morse (S.) & Fitch (C. M.), J. Lab. & Clin. M. (St. Louis), 1923, **8**, 692-695.

The Kottmann reaction is susceptible to considerable error unless the carbon dioxide content and other variables are taken into account.—I. B.

Endemic goiter (Il gozzo endemico). Muccia (G.), Med. ital. (Milano), 1923, **4**, 317-325.

Review of the etiology, pathogenesis and treatment of goiter on the basis of the theory of iodine insufficiency. The author proposes the iodization of common kitchen salt, as is done in Switzerland.—P. M. N.

An unusual condition of one eye in a case of exophthalmic goiter. Myers (B.), Proc. Roy. Soc. Med. (Lond.), 1924, **17**, 13-14 (Clin. Sect.).

In a woman of 42 with exophthalmic goiter of about 9 years' duration, a severe blow on the right side of the nose resulted in immediate disappearance of exophthalmos of the right eye, with remaining unilateral exophthalmos. Now, after 3 years, the right eye is again somewhat prominent. It is believed that the disappearance of exophthalmos after the blow was due to "inhibition of the action of the muscle fibers of Müller to lose their contraction," while at the present time the muscle fibers are contracting again.—I. B.

An experimental study of mitochondrial changes in the thyroid gland. Nicholson (F. M.), J. Exper. Med. (Balt.), 1924, **39**, 63-76.

A fairly large number of normal guinea pigs and rabbits was divided into groups and each group subjected to one of the following procedures: interference with thyroid circulation, partial extirpa-

tion of the thyroid gland, fasting, thyroid feeding, withholding of the water-soluble vitamine from the diet, inhalation of oxygen, nitrogen, hydrogen or carbon dioxide gas, administration of atropine, pilocarpine, adrenalin, potassium arsenite or hydrogen cyanide. Normal control animals were observed at intervals over a period of 4 months to have no changes in the mitochondria. At intervals of a few days individual animals in the various series were examined with regard to the mitochondrial changes in the thyroid cells. All thyroid tissue was first fixed in the following mixture devised by Pianese: 1% aqueous solution of sodium platinic chloride, 15 cc.; ¼% aqueous solution chromic acid, 5 cc.; 2% aqueous solution osmic acid, 5 cc.; formic acid C. P., 1 drop. The gland was then examined in section for mitochondria. Fragmentation of mitochondrial filaments into granules was found to follow most of the above procedures. Reduction in the number of mitochondria was observed coincidently with this change. The number of mitochondria was increased in the cases with compensatory thyroid hypertrophy following removal of some three-fourths of the thyroid tissue.—I. M.

Operative results of thyroidectomy and thymectomy in the rabbit. Pearce (Louise) & Van Allen (C. M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 319-320.

This is a report on the operative mortality. Thymectomy does not affect the animals while thyroidectomy results in lowered resistance to various things including syphilis and transplantable malignant tumors.—J. C. D.

Goiter survey in Wexford County, Michigan. Pub. Health Rep. (Wash.), 1924, **39**, 663-664.

Of the total number of boys and girls examined, 2247 were in the city of Cadillac, where thyroid enlargement was found to be present in 50.4%. Of the boys examined in Cadillac, 41.8% were found to have thyroid enlargement; and of the girls, 58.0%. In the rural and village schools of Wexford County outside of Cadillac, 62.2% of the children were found with thyroid enlargement—54.2% of the boys and 71.0% of the girls. The water supply of the city of Cadillac shows a very slight trace of iodine, whereas no iodine is found in the water in the rural districts of the county. The average city dweller probably has more opportunities to secure iodine in his food supply than has the rural dweller, on account of his somewhat more varied diet. Sea foods, ordinarily only infrequently supplied to rural districts, are more common in the markets of the city. Another possible factor mentioned is that medical treatment is more generally available in the city than in the country.—R. G. H.

Comparison of the oxygen consumption of surviving organs of mammals in the normal condition and after feeding with thyroid (Bei-

träge zur Physiologie der Drüsen. 61. L. Asher. Vergleich des Sauerstoffcerbrauchs überlebender Säugetierorgane im normalen Zustande und nach Fütterung mit Schilddrüsenhormon). Rohrer (A.), Biochem. Ztschr. (Berl.), 1924, **145**, 154-167.

The liver, kidney, and muscle tissues of mice were used in these studies. It was found that previous feeding of the animals with thyroid preparations enhanced the oxygen consumption of the surviving organs.—F. S. H.

The Kottmann reaction in the insane. Saunders (A. M.), J. Lab. & Clin. M. (St. Louis), 1924, **9**, 401-403.

The author finds the Kottmann test of greater value than basal metabolism determinations in the diagnosis of thyroid disturbances in the insane.—I. B.

Kottmann's photo-reaction as evidence of thyroid function (Beiträge zur klinischen Konstitutionspathologie. X. Zur Bewertung der Kottmannschen "Photoreaktion" als Funktionsprüfung der Schilddrüse). Schur (M.), Ztschr. f. Konstit. (Berl.), 1923, **9**, 412.

After testing 8 patients with exophthalmic goiter, 3 with myxedema and 1 imbecile with hypothyroidism, Schur concluded that Kottmann's photo-reaction (1 cc. fresh serum plus 0.25 cc. 0.5% potassium iodide and 0.3 cc. 0.5% silver nitrate solution, exposed to the light and developed with 0.5 cc. 0.25% hydrochinon) is not a reliable indicator of thyroid activity.—A. T. R.

Immediate effect of subtotal thyroidectomy in toxic goiter. Segall (H. N.) & Means (J. H.), Arch. Surg. (Chicago), 1924, **8**, 176-188.

It is generally recognized that the clinical improvement following successful subtotal thyroidectomy is a relatively rapid one. Segall and Means express this improvement precisely by means of daily basal metabolism and pulse rate curves, and thus show the actual rate of detoxication in quantitative terms. From the studies reported, it is concluded that the rate of detoxication following subtotal thyroidectomy is quite similar to that during recovery from hyperthyroidism induced by thyroid feeding. The time required for detoxication depends on the intensity of the preoperative intoxication. While pulse and basal metabolism show considerable parallelism, the latter fluctuates less and is the better index of the degree of hyperthyroidism. The slight rise in pulse and metabolism which is usual just before operation is due to emotional tension, and very likely a resulting increase in liberation of epinephrin.

—J. Am. M. Ass., **82**, 822.

Congenital goiter. Skinner (H. H.), J. Am. M. Ass. (Chicago), 1924, **82**, 1190-1192.

Twelve cases are reported. The author concludes that congenital goiters are more common than it has been ordinarily supposed. They are caused by iodin deficiency in the mother's diet. All grades of pathologic change may be seen, from a simple parenchymatous goiter with no symptoms, to marked enlargement with complete tracheal compression and cystic conditions causing serious danger to mother and child. Treatment is surgical for emergencies, but mainly prophylactic by means of iodin administration to the mother.—R. G. H.

The effect of treatment in hyperthyroidism controlled by observations of the basal metabolic rate. Trumble (H. C.), Med. J. Australia (Sydney), 1924, **i**, 131-135 (Suppl.).

Trumble reports a number of cases of exophthalmic goiter and toxic adenoma (not differentiated) divided in 4 groups as follows: Group I—Two cases treated by half-hearted medical measures, such as the hospital out-patient department treatment. Group II—Seven cases receiving careful medical treatment, with prolonged rest in bed. Group III—Five treated by exposure to x-rays. Group IV—Twelve subjected to operation. He concludes that exophthalmic goiter and toxic adenoma of the thyroid gland are diseases which tend to progress to the detriment of all tissues of the body; the heart and nervous system suffer more especially. The most effective measures at present available in the treatment of these cases are rest, x-rays and partial thyroidectomy. Rest is but rarely sufficient, though generally followed by slight improvement. Treatment by x-rays in this series was not generally successful, but in certain cases is probably of great use. Removal of one lobe is usually followed by great improvement, but recurrence of symptoms appears to be common. Radical removal of two-thirds to five-sixths of the gland offers the best chance of cure at present available.

—R. G. H.